

Update on Syphilis

Resurgence of an Old Problem

Matthew R. Golden, MD, MPH

Christina M. Marra, MD

King K. Holmes, MD, PhD

IN 1937 US SURGEON GENERAL Thomas Parran estimated that 10% of Americans would be infected with syphilis during their lives.¹ Rates of primary and secondary syphilis plummeted with the institution of public health control measures and the advent of penicillin, reaching a nadir in 2000. Since then, rates have continued to decline among women and infants, although overall rates again have begun to climb.²

The dominant epidemiological features of syphilis in the United States today include varying incidence rates by geography, race and sexual orientation, and an association with human immunodeficiency virus (HIV). Syphilis rates among heterosexuals in the United States are highest in the south, where 16 states reported 53% of all US cases in 2001, including 64% of all cases in women.² Syphilis disproportionately affects blacks. In 2001, reported US rates of primary and secondary syphilis were 42 times higher among black women than among white women.² Racial disparities likely reflect not only bias in syphilis reporting and differential access to medical care but also racial segregation in sexual activity, and other differences in sexual networks between ethnic groups.³

Since 1997, increases in syphilis rates among men who have sex with men have been documented in Seattle, Chicago, southern California, San Fran-

cisco, New York, Miami, Boston, and several European and Canadian cities.⁴ Rates of other sexually transmitted diseases (STDs) also have risen among men who have sex with men, reflecting a general increase in unsafe sexual behavior with the availability of potent antiretroviral therapy for HIV.⁵ Although national reporting does not capture information about sexual orientation, in 2001 the estimated rate per 100 000 of primary and secondary syphilis in King County, Washington was 141 among men who have sex with men, 683 among men who have sex with men infected with HIV, and less than 1 among heterosexuals (H.H. Handsfield, oral communication, April 2003). Cities in the United States have reported that 20% to 73% of men who have sex with men with syphilis are HIV-infected⁶ vs a median HIV seroprevalence of 12.5% among women with syphilis in studies published between 1995 and 1998.⁷ Epidemiologic studies and studies documenting increased HIV shedding associated with genital ulcers strongly suggest that syphilis increases both the susceptibility of infected persons to HIV acquisition and the likelihood that dually infected persons transmit HIV to their sex partners.⁸

Clinical Manifestations

Syphilis passes through a series of frequently overlapping stages.⁹ *Treponema pallidum*, a spirochete, causes syphilis and is spread through contact with infectious lesions or body fluids. Studies from the preantibiotic era typically found that 50% to 75% of exposed sex partners of persons with primary or secondary syphilis were infected, and that among contacts without clinical or serological evidence of

infection on initial evaluation, approximately 30% developed syphilis in the absence of treatment.¹²

Patients typically develop a skin lesion (chancre) at the site of inoculation approximately 21 days after exposure. Chancres frequently go unnoticed, particularly among women and men who have sex with men who may not be able to see vaginal or anal lesions. **BOX 1** presents the differential diagnosis for genital ulcer disease (GUD). Herpes causes most GUD in the United States. In 2000, more than 2 million Americans sought care for genital herpes, whereas only 5979 cases of primary and secondary syphilis and 82 cases of chancroid were reported to the Centers for Disease Control and Prevention (CDC). Syphilitic chancres are classically nontender, indurated, non-purulent ulcers. However, a study of men with GUD revealed the presence of that triad in only 31% of syphilis patients; induration was 95% specific but only 47% sensitive.¹³ Both syphilitic chancres and herpetic lesions heal without therapy.

Signs and symptoms of secondary syphilis typically begin 4 to 10 weeks after the appearance of a chancre. Rash is the presenting complaint in more than 70% of patients with secondary syphilis and is found on physical examination in more than 90% of patients.^{10,14} A macular rash, the earliest

Author Affiliations: Division of Infectious Diseases, the Center for AIDS and STD (Drs Golden, Marra, and Holmes) and Department of Neurology (Dr Marra), University of Washington, Seattle, and Public Health-Seattle and King County (Dr Golden), Seattle, Wash.
Corresponding Author: Matthew R. Golden, MD, MPH, Harborview Medical Center, Box 359777, 325 Ninth Ave, Seattle, WA 98104 (e-mail: golden@u.washington.edu).

Contempo Updates Section Editor: Sarah Pressman Lovinger, MD, Fishbein Fellow.

CME available online at
www.jama.com

and most common finding, is characterized by 3- to 10-mm pink-, red-, or copper-colored macules variously distributed on the flanks, shoulders, arms, chest, and back. Untreated, the macules can become maculopapular or papulosquamous, affecting the hands and/or soles in 50% to 80% of cases.^{14,15} The rash of secondary syphilis also can be pustular, annular, or follicular, but virtually never vesicular.

Box 1 presents the differential diagnosis for the rash of secondary syphilis. Other symptoms and signs commonly include sore throat, malaise, headache, and lymphadenopathy, and less commonly include fever, meningismus, myalgias, weight loss, anorexia, hair loss, arthralgias, mucous patches, condyloma lata, and ocular complaints. Secondary syphilis is a systemic process and can cause neurologic, renal, ophthalmologic, gastrointestinal, and hepatic disease.

Secondary syphilis resolves without treatment, although approximately one quarter of untreated patients develop recurrences during the 4 years following infection, most frequently in the first year.⁹ The CDC differentiates early and late latent syphilis as asymptomatic infection during the first year following infection and during the period thereafter, respectively. Approximately one third of patients with untreated syphilis develop late sequelae (FIGURE).^{9-11,16}

HIV Infection and Syphilis

Case reports and retrospective studies suggest that HIV may alter the clinical presentation and natural history of syphilis. These studies describe persistent chancres, ulcerative skin lesions, rapid progression to gummatous disease characterized by destructive lesions of the skin, bones or viscera, and a greater frequency of ocular involvement, neurosyphilis, treatment failure, and relapse.¹⁷ While a prospective trial observed that HIV-infected patients with early syphilis were more likely than persons without HIV to have multiple chancres, delayed chancre healing, cerebrospinal fluid (CSF) abnormal findings, and serological treatment failure, only

a single case of clinical treatment failure occurred among 101 HIV-infected patients.^{14,18} The size of that study and the absence of data on patients' CD4 cell counts do not allow for the exclusion of the possibility that HIV, particularly late immunosuppression, is associated with a clinically significant increase in the risk of poor outcomes. However, it appears that the risk is less than that suggested by earlier reports and that most patients will respond to standard treatment.

Laboratory Diagnosis

Treponema pallidum cannot be cultured. Darkfield examination and direct fluorescent antibody stains of exudates from genital ulcers or mucocutaneous lesions provide direct evidence of infection, but are insensitive and not widely available. In the United States, patients suspected of having syphilis initially are tested using a nontreponemal serologic test (rapid plasma reagin [RPR], VDRL), with positive results confirmed using a treponemal-specific test (*T pallidum* particle agglutination [TPPA], fluorescent treponemal antibodies [FTA-abs]).^{19,20} Nontreponemal tests are 78% to 86% sensitive in primary syphilis, virtually 100% sensitive in secondary syphilis, and 95% to 98% in latent syphilis. False-positive results for nontreponemal tests occur in 1% to 2% of the US population and are associated with autoimmune disease, injection drug use, tuberculosis, vaccinations, pregnancy, infectious mononucleosis, HIV, rickettsial infections, spirochetal infections other than syphilis, and bacterial endocarditis; titers are 1:8 or lower in 90% of cases. Persons with very high titer RPR or VDRLs may have false-negative test results that become positive with serum dilution (prozone phenomenon). Causes of false-positive results for treponemal tests include other spirochetal infections, malaria, and leprosy. Human immunodeficiency virus can cause false-negative results in nontreponemal and treponemal tests.^{21,22} Although clinicians traditionally have been taught that nontreponemal test results become negative after

Box 1. Differential Diagnosis of Syphilis

Primary syphilis—genital ulcer disease

- Genital herpes
- Chancroid
- Aphthous ulcer
- Lymphogranuloma venereum
- Donovanosis
- Superinfection of ectoparasitic infections
- Trauma
- Neoplasm
- Autoimmune diseases: Behçet syndrome, Crohn disease, Reiter syndrome
- Fixed drug eruptions: doxycycline, sulfonamides, nonsteroidal anti-inflammatory drugs

Secondary syphilis—rash

- Primary HIV
- HIV immune reconstitution syndrome
- Pityriasis rosea
- Psoriasis
- Erythema multiforme
- Tinea versicolor
- Lichen planus
- Drug eruption
- Viral exanthema
- Scabies
- Streptococcal or *Arcanobacterium haemolyticum* pharyngitis

treatment and that treponemal test results remain positive for life, a study of 857 syphilis patients found that 28% of those with primary syphilis and 44% with secondary syphilis had persistently positive nontreponemal test results 36 months after treatment; among persons with first-episode primary syphilis, 87% and 76% had persistently positive results for microhemagglutination assay for *T pallidum* (MHA-TP) and FTA-abs tests, respectively.²³

Central Nervous System Syphilis

Treponema pallidum invades the central nervous system (CNS) early in syphilis and is demonstrated by CSF pleocytosis or elevated protein concentration, reactive CSF-VDRL, or identification of *T pallidum* in CSF by PCR

or by infectivity of CSF in rabbits.²⁴ In the preantibiotic era, about 25% of patients did not clear CNS organisms. Few immunocompetent individuals fail to clear CSF abnormalities after penicillin treatment.²⁵ Persons who have persistent organisms in the CNS are at risk for symptomatic neurosyphilis.

Neurosyphilis can be divided into early and late forms.²⁶ Early neurosyphilis affects the CSF, cerebral blood vessels, and meninges more often than brain or spinal cord parenchyma. It occurs within weeks to a few years after primary infection, can coexist with primary and secondary syphilis, and may be asymptomatic. Symptomatic forms of early neurosyphilis include meningitis, with or without cranial nerve or

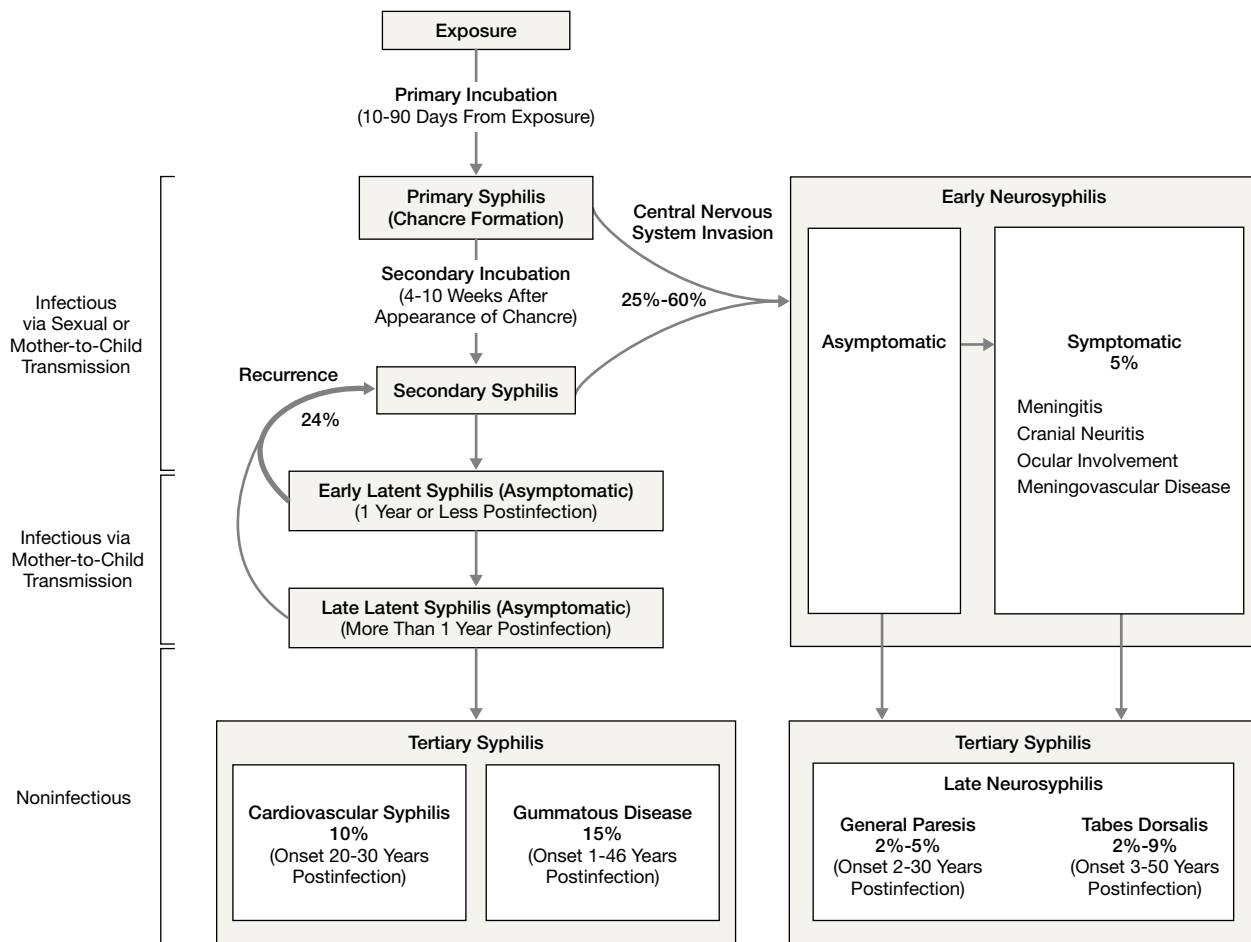
eye involvement, and meningovascular disease or stroke. Late neurosyphilis affects the meninges and brain or spinal cord parenchyma, is extremely rare in the antibiotic era, and usually occurs years to decades after primary infection. Manifestations of late neurosyphilis include general paresis, a rapidly progressive dementia with psychotic features, and tabes dorsalis, a spinal cord disorder with sensory ataxia and bowel and bladder dysfunction.

Criteria for performance of lumbar puncture in patients with syphilis are intended to select those at greatest risk for neurosyphilis. The CDC criteria include any 1 of the following: (1) neurologic or ocular symptoms or signs; (2) late latent syphilis or syphilis of un-

known duration in a patient with HIV; (3) active tertiary syphilis (eg, gumma, aortitis, or iritis); or (4) treatment failure for nonneurologic syphilis.²⁷ Some authorities suggest performing a lumbar puncture on all patients with HIV and syphilis. A recent study found that persons with serum nontreponemal test titers 1:32 or higher and HIV-infected persons with CD4 cell counts 350/ μ L or lower were at higher risk of CNS syphilis.²⁸ The risk of neurologic sequelae in HIV-infected patients with early syphilis and CSF abnormal findings following therapy with benzathine penicillin is unknown.

Interpretation of CSF findings is complicated by the absence of a criterion standard for the diagnosis of neuro-

Figure. Natural History of Untreated Syphilis in Immunocompetent Individuals



Percentages of individuals developing specific stages of syphilis and time intervals are approximations based on information in references 9-11.

syphilis and the fact that many patients with syphilis have HIV, an infection associated with pleocytosis during primary infection and an elevated CSF protein level in late disease. In the absence of visible blood contamination, a positive CSF-VDRL result is specific and establishes the diagnosis of neurosyphilis; however, the sensitivity of CSF-VDRL against clinical diagnosis is only 30% to 70%.²⁰ In contrast, treponemal tests are sensitive, but nonspecific; a negative CSF-FTA-abs result virtually excludes the diagnosis of neurosyphilis.²⁹ We treat asymptomatic HIV-infected patients for neurosyphilis if they have a positive CSF-FTA-abs result and a CSF pleocytosis (>5 white blood cells per mm³), and asymptomatic HIV-uninfected patients if they have a positive CSF-FTA-abs result and either a CSF pleocytosis or an elevated CSF protein level (>45 mg/dL).

Treatment and Follow-up

BOX 2 presents CDC's recommended treatments for syphilis.²⁷ Nonrandomized trials in which patients with primary or secondary syphilis were followed up for 1 year or longer after penicillin treatment have reported re-treating 5% to 11% of patients, generally because of failure of nontreponemal tests to show an adequate decline in titer.³⁰⁻³² The efficacy of recommended therapies for latent syphilis and neurosyphilis is supported by clinical experience rather than by controlled trials.

Small studies have found that azithromycin is as effective as benzathine penicillin in incubating syphilis and possibly adequate for primary and secondary syphilis.^{33,34} Ceftriaxone was effective for neurosyphilis in a small trial involving HIV-1-infected patients.²⁶ However, available data do not yet warrant recommending either azithromycin or ceftriaxone as standard treatments.

All syphilis patients require clinical and serological follow-up 6 and 12 months after treatment. Patients infected with HIV also should be evaluated at 3, 9, and 24 months following treatment. Treatment failure is defined as persistent signs or symptoms

Box 2. Centers for Disease Control and Prevention Recommended Treatments for Syphilis²⁷

Primary, secondary, or early latent syphilis*

Recommended: benzathine penicillin G, 2.4 million units in a single dose, intramuscularly

Penicillin allergy: doxycycline, 100 mg by mouth twice daily for 14 days

Late latent syphilis, syphilis of unknown duration, tertiary syphilis

Recommended: benzathine penicillin G, 2.4 million units weekly for 3 weeks, intramuscularly

Penicillin allergy: doxycycline, 100 mg by mouth twice daily for 28 days

Neurosyphilis, syphilitic eye disease, syphilitic auditory disease

Recommended: Aqueous crystalline penicillin G, 18-24 million units per day administered as 3-4 million units intravenously every 4 hours or continuous infusion for 10-14 days

Alternative: procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg by mouth 4 times a day, both for 10-14 days†

*Latent syphilis is defined as seroreactivity without other evidence of disease. Early latent syphilis is diagnosed in patients infected within the preceding year as defined by 1 of the following: (1) a documented seroconversion; (2) unequivocal symptoms of primary or secondary syphilis; or (3) a sex partner documented to have primary, secondary, or early latent syphilis. Pregnant women should not be treated with doxycycline.

†Patients with non-life-threatening allergies to penicillin should ideally be desensitized. Patients with serious allergies to sulfonamides should not be treated with probenecid-containing regimens.

or failure of nontreponemal test titers to decline 4-fold (2 dilutions) within 6 months of treatment or a sustained 4-fold increase in nontreponemal test titer after treatment. Patients who do not respond to therapy should undergo CSF examination and retreatment, either for neurosyphilis or late latent syphilis as indicated by CSF test results. Patients with neurosyphilis should have a repeat CSF examination 3 to 6 months following therapy and then every 6 months until the CSF test result is normal. Patients treated for syphilis should be tested for HIV and other STDs, such as gonorrhea and chlamydial infections.

Prevention and Elimination of Syphilis

Since 1998, the CDC has led an ongoing effort to eliminate syphilis from the United States. The decline in syphilis rates among US women using largely conventional public health methods of enhanced surveillance, screening, and partner notification as well as collaboration with community-based organi-

zations is encouraging,² although the persistence of relative racial disparities in disease, recent increases in syphilis in Eastern Europe, and an ongoing outbreak in Vancouver, British Columbia, that did not abate following a targeted mass treatment program demonstrate the continued challenges to eliminating syphilis among heterosexuals.^{35,36}

Epidemic syphilis among men who have sex with men is now the dominant obstacle to the goal of eliminating syphilis. Conventional methods have not controlled this epidemic.^{6,37} Although enhanced screening in venues such as jails and bathhouses has identified cases, similar programs have not contained syphilis epidemics among men who have sex with men in the past and seem unlikely to do so now.³⁸ Other individual-level behavioral interventions among men who have sex with men have reduced self-reported rates of unprotected anal intercourse,³⁹ but have not been shown to reduce rates of STDs nor have they been instituted on a scale sufficient to have a significant impact at the population level. New diagnostic tests, therapeutics, and

prevention approaches are needed. Diagnostics based on PCR, less invasive (eg, oral fluid) tests, rapid point-of-care tests, and serologic tests that differentiate active and adequately treated infections are diagnostic priorities. Defining the efficacy of azithromycin for early syphilis might simplify therapy. Recently iden-

tified *T pallidum* immunogens may prove useful for vaccine development.⁴⁰ Finally, innovative structural interventions—efforts to alter the physical, social, cultural, and legal environment in which risk occurs—could alter the availability, acceptability, and accessibility of behaviors and materials that affect risk⁴¹;

to date, little research has been done in the United States to develop and evaluate such interventions for STD prevention.

Funding/Support: Dr Golden is supported by NIH grant K23 AI01846-02.

Acknowledgment: We thank Hillard Weinstock, MD, for providing us with US national syphilis data.

REFERENCES

- Parran T. *Shadow on the Land*. New York, NY: Reynal & Hitchcock; 1937.
- Centers for Disease Control and Prevention, National Center for HIV, STD and TB Prevention, Division of Sexually Transmitted Diseases. *Sexually Transmitted Diseases Surveillance 2001*. Atlanta, Ga: CDC; September, 2002.
- Laumann EO, Youm Y. Racial/ethnic group differences in the prevalence of sexually transmitted diseases in the United States: a network explanation. *Sex Transm Dis*. 1999;26:250-261.
- Ciesielski CA. Sexually transmitted diseases in men who have sex with men: an epidemiologic review. *Curr Infect Dis Rep*. 2003;5:145-152.
- Katz MH, Schwarcz SK, Kellogg TA, et al. Impact of highly active antiretroviral treatment on HIV seroprevalence among men who have sex with men: San Francisco. *Am J Public Health*. 2002;92:388-394.
- Primary and secondary syphilis among men who have sex with men—New York City, 2001. *MMWR Morb Mortal Wkly Rep*. 2002;51:853-856.
- Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis*. 2000;27:53-59.
- Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. *Sex Transm Infect*. 1999;75:3-17.
- Clark G, Danbolr N. The Oslo study of the natural course of untreated syphilis: an epidemiologic investigation based on re-study of the Boeck-Bruusgaard material. *Med Clin North Am*. 1964;48:613-623.
- Stokes J, Beerman H, Ingraham N. *Modern Clinical Syphilology*. 3rd ed. Philadelphia, Pa: WB Saunders Co; 1945.
- Merritt H, Adams R, Solomon H. *Neurosyphilis*. New York, NY: Oxford University Press; 1940.
- Garnett GP, Aral SO, Hoyle DV, Cates W Jr, Anderson RM. The natural history of syphilis: implications for the transmission dynamics and control of infection. *Sex Transm Dis*. 1997;24:185-200.
- DiCarlo RP, Martin DH. The clinical diagnosis of genital ulcer disease in men. *Clin Infect Dis*. 1997;25:292-298.
- Rompalo AM, Joesoef MR, O'Donnell JA, et al. Clinical manifestations of early syphilis by HIV status and gender: results of the syphilis and HIV study. *Sex Transm Dis*. 2001;28:158-165.
- Hutchinson CM, Hook EW 3rd, Shepherd M, Verley J, Rompalo AM. Altered clinical presentation of early syphilis in patients with human immunodeficiency virus infection. *Ann Intern Med*. 1994;121:94-100.
- Rosahn P. Autopsy studies of syphilis. *J Vener Dis*. 1947;649(suppl 21):1-67.
- Collis TK, Celum CL. The clinical manifestations and treatment of sexually transmitted diseases in human immunodeficiency virus-positive men. *Clin Infect Dis*. 2001;32:611-622.
- Rolfs RT, Joesoef MR, Hendershot EF, et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection: the Syphilis and HIV Study Group. *N Engl J Med*. 1997;337:307-314.
- Hart G. Syphilis tests in diagnostic and therapeutic decision making. *Ann Intern Med*. 1986;104:368-376.
- Larsen S, Kraus S, Whittington W. Diagnostic tests. In: Larsen SA, Hunter E, Kraus S, eds. *A Manual of Tests for Syphilis*. Washington, DC: American Public Health Association; 1990:2-26.
- Hicks CB, Benson PM, Lupton GP, Tramont EC. Seronegative secondary syphilis in a patient infected with the human immunodeficiency virus (HIV) with Kaposi sarcoma: a diagnostic dilemma. *Ann Intern Med*. 1987;107:492-495.
- Erbelding EJ, Vlahov D, Nelson KE, et al. Syphilis serology in human immunodeficiency virus infection: evidence for false-negative fluorescent treponemal testing. *J Infect Dis*. 1997;176:1397-1400.
- Romanowski B, Sutherland R, Fick GH, Mooney D, Love EJ. Serologic response to treatment of infectious syphilis. *Ann Intern Med*. 1991;114:1005-1009.
- Lukehart SA, Hook EW 3rd, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by *Treponema pallidum*: implications for diagnosis and treatment. *Ann Intern Med*. 1988;109:855-862.
- Fernando WL. Cerebrospinal fluid findings after treatment of early syphilis with penicillin: a further series of 80 cases. *Br J Vener Dis*. 1968;44:134-135.
- Marra CM, Boutin P, McArthur JC, et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. *Clin Infect Dis*. 2000;30:540-544.
- Sexually transmitted treatment guidelines 2002: Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 2002;51(RR-6):1-78.
- Marra C, Maxwell C, Smith S, et al. Risk factors for neurosyphilis. Paper presented at: 2002 National STD prevention conference, 2002; San Diego, Calif.
- Marra CM, Critchlow CW, Hook EW 3rd, Collier AC, Lukehart SA. Cerebrospinal fluid treponemal antibodies in untreated early syphilis. *Arch Neurol*. 1995;52:68-72.
- Schroeter AL, Lucas JB, Price EV, Falcone VH. Treatment for early syphilis and reactivity of serologic tests. *JAMA*. 1972;221:471-476.
- Elliott WC. Treatment of primary syphilis. *J Am Vener Dis Assoc*. 1976;3(2 pt 2):128-135.
- Brown ST. Treatment of secondary syphilis. *J Am Vener Dis Assoc*. 1976;3(2 pt 2):136-142.
- Hook EW 3rd, Stephens J, Ennis DM. Azithromycin compared with penicillin G benzathine for treatment of incubating syphilis. *Ann Intern Med*. 1999;131:434-437.
- Hook EW 3rd, Martin DH, Stephens J, Smith BS, Smith K. A randomized, comparative pilot study of azithromycin versus benzathine penicillin G for treatment of early syphilis. *Sex Transm Dis*. 2002;29:486-490.
- Riedner G, Dehne KL, Gromyko A. Recent declines in reported syphilis rates in eastern Europe and central Asia: are the epidemics over? *Sex Transm Infect*. 2000;76:363-365.
- Rekart ML, Patrick DM, Chakraborty B, et al. Targeted mass treatment for syphilis with oral azithromycin. *Lancet*. 2003;361:313-314.
- Bellis MA, Cook P, Clark P, Syed Q, Hoskins A. Re-emerging syphilis in gay men: a case-control study of behavioural risk factors and HIV status. *J Epidemiol Community Health*. 2002;56:235-236.
- Wolf FC, Judson FN. Intensive screening for gonorrhea, syphilis, and hepatitis B in a gay bathhouse does not lower the prevalence infection. *Sex Transm Dis*. 1980;7:49-52.
- Johnson WD, Hedges LV, Diaz RM. Interventions to modify sexual risk behaviors for preventing HIV infection in men who have sex with men. *Cochrane Database Syst Rev*. 2003(1):CD001230.
- Morgan CA, Lukehart SA, Van Voorhis WC. Immunization with the N-terminal portion of *Treponema pallidum* repeat protein K attenuates syphilitic lesion development in the rabbit model. *Infect Immun*. 2002;70:6811-6816.
- Blankenship KM, Bray SJ, Merson MH. Structural interventions in public health. *AIDS*. 2000;14(suppl 1):S11-21.