

# Centers for Disease Control and Prevention Sexually Transmitted Diseases Treatment Guidelines

Kimberly A. Workowski<sup>1,2</sup> and Stuart M. Berman<sup>1</sup>

<sup>1</sup>Division of STD Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention (proposed), Centers for Disease Control and Prevention, and <sup>2</sup>Division of Infectious Diseases, Emory University, Atlanta, Georgia

Sexually transmitted diseases (STDs) constitute an epidemic of tremendous magnitude, with an estimated 18.9 million persons acquiring a new STD each year [1]. Reported disease rates underestimate the true burden of infection because the majority of STDs are asymptomatic and because of underreporting. STDs have far-reaching public health consequences for the sexual and reproductive health of individual persons, as well as for the long-term health and health care costs of the community.

The accurate identification and the effective clinical management of STDs represent an important combined strategy necessary to improve reproductive and sexual health and to improve HIV prevention efforts. This is especially relevant to women, adolescents, and infants, because untreated infections frequently result in severe, long-term complications, including facilitation of HIV infection, tubal infertility, adverse pregnancy outcomes, and cancer. For >20 years, the publication of national guidelines by the Centers for Disease Control and Prevention

(CDC) for the management of STDs has assisted clinicians with effective guidance on the delivery of optimal STD care. The CDC STD treatment guidelines are the most widely referenced and authoritative source of information on STD treatment and prevention strategies for clinicians who evaluate persons with STDs or those at risk for STDs.

The 2006 CDC guidelines for the treatment of sexually transmitted diseases were developed in consultation with public- and private-sector professionals knowledgeable in the management of STDs [2]. An evidence-based systematic review was performed, focusing on peer-reviewed journal articles and abstracts that had become available since publication of the 2002 CDC STD treatment guidelines. Evidence tables were developed from systematic reviews that summarized the study type, population and setting, treatment regimens or other interventions, outcome measures, and potential limitations of the reported findings. This supplement to *Clinical Infectious Diseases* contains 9 background articles that describe the available evidence in several topic areas included in the 2006 CDC STD treatment guidelines. Current advances and controversies are described in the diagnosis, management, and treatment of various sexually transmitted pathogens and syndromes that have important implications for clinical practice.

*Chlamydia trachomatis* infection is the

most common bacterial STD in the United States, with an estimated 3 million cases occurring annually [3]. Reported rates of chlamydial infection have increased dramatically over the past decade, reflecting expansion of chlamydial screening activities, highly sensitive nucleic acid amplification tests, and improvements in information systems used for reporting. However, many women who are at risk for this infection are still not being screened appropriately, reflecting, in part, a lack of awareness among some providers, as well as limited resources. Health care providers frequently rely on screening tests, because asymptomatic infection is common among both men and women. Annual screening of all sexually active women  $\leq 25$  years of age is recommended [4], as is screening of older women with risk factors (e.g., those who have a new sex partner or multiple sex partners). There is insufficient evidence to recommend routine screening for *C. trachomatis* in sexually active young men on the basis of feasibility, efficacy, and cost-effectiveness; however, screening should be considered in high-prevalence areas, such as adolescent clinics, correctional facilities, and STD clinics. Efficacious therapeutic regimens for chlamydia include azithromycin or doxycycline. Because of the high probability of repeat infection, women should be retested for chlamydial infection 3–4 months after treatment [5]. Clinical experience and limited studies are avail-

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Reprints or correspondence: Dr. Kimberly A. Workowski, Centers for Disease Control and Prevention, Mailstop E-02, 1600 Clifton Rd., Atlanta, GA 30333 (kgw2@cdc.gov).

**Clinical Infectious Diseases** 2007;44:S73–6

© 2007 by the Infectious Diseases Society of America. All rights reserved.

1058-4838/2007/4407S3-0001\$15.00

DOI: 10.1086/511430

able to support the efficacy and safety of azithromycin as a recommended regimen in pregnant women.

Infections with *Neisseria gonorrhoeae* account for the second most commonly notifiable disease in the United States [3] and are an important cause of cervicitis, urethritis, proctitis, and pelvic inflammatory disease. Selection of appropriate therapy for gonorrhea is guided by a CDC-sponsored surveillance system (Gonococcal Isolate Surveillance Project) that has monitored gonococcal antimicrobial susceptibility for the past 20 years. Of recent concern, the prevalence of quinolone-resistant *N. gonorrhoeae* has increased in many areas of the United States and among men who have sex with men, resulting in changes in recommended treatment regimens. The CDC Web site [6] or state and local health departments can provide the most current information on quinolone-resistant *N. gonorrhoeae* prevalence. Because prevalence can vary greatly by location, state and local public health officials should maintain the capacity to detect and monitor the prevalence of resistant strains. Oral alternatives to quinolones are limited, because the manufacture of cefixime tablets was discontinued in 2002 (generic suspension available: 100 mg/5 mL). Some evidence suggests that cefpodoxime proxetil or cefuroxime axetil might be reasonable oral alternative regimens.

Cervicitis is a common finding among women in a variety of clinical settings. However, there are no reliable population-based data to accurately estimate prevalence, nor is there a consensus in the scientific literature on a standard definition. An inconsistent definition of cervicitis limits the translation of clinical research outcomes into guidance for clinical management. *C. trachomatis*, *N. gonorrhoeae*, *Trichomonas vaginalis*, and genital herpes are established etiologic agents for cervicitis, and limited data suggest an association with bacterial vaginosis and *Mycoplasma genitalium*. However, in the majority of cases of cervicitis, no pathogen

is identified. The evaluation of cervicitis should include nucleic acid amplification testing on cervical or urine specimens for chlamydia and gonorrhea and examination of vaginal secretions for bacterial vaginosis and trichomoniasis. The decision to provide presumptive therapy for cervicitis (chlamydia or gonorrhea) should include an individual risk assessment, the likelihood of follow-up, and the prevalence of infection in the population [7]. However, there is limited information on the natural history of cervicitis when neither chlamydia nor gonorrhea is present. The value of prolonged administration of antibiotic therapy for cervicitis is unknown, because standard management options are undefined. Research efforts are needed to explore the role of other determinants that may cause cervicitis, including fastidious pathogens, persistent abnormalities of the vaginal flora, idiopathic inflammation, or an altered local host immune response.

Pelvic inflammatory disease is diagnosed in ~1 million women each year and can be associated with serious reproductive complications, including ectopic pregnancy, infertility, and chronic pelvic pain [8]. Sexually transmitted organisms, especially *C. trachomatis* and *N. gonorrhoeae*, aerobic and anaerobic vaginal flora, and genital mycoplasmas, have been associated with pelvic inflammatory disease. Several broad-spectrum antimicrobial regimens have demonstrated clinical and microbiological effectiveness in randomized clinical trials; however, only a limited number of these studies have determined the incidence of long-term complications (tubal infertility and ectopic pregnancy) after antimicrobial administration. Recent data have demonstrated no differences in short- and long-term clinical and microbiological response rates between parenteral or oral therapy [9]. Further research is needed to explore the importance of anaerobic bacteria in the pathogenesis of pelvic inflammatory disease, because there are no definitive data demonstrating the superiority of antimicrobial regimens that

include anaerobic coverage. Additionally, resistance to clindamycin has recently been observed among lower genital tract isolates [10], which may be of concern because clindamycin has been a well-established component of successful regimens for pelvic infections.

*T. vaginalis* infection is one of the most common sexually transmitted infections, with an estimated 5–7 million incident infections occurring annually in the United States [1]. Metronidazole or tinidazole is the recommended regimen for trichomoniasis treatment. Tinidazole (approved by the US Food and Drug Administration in May 2004) provides a therapeutic option with a long serum half-life, high concentrations in genitourinary tissues, and low MICs, but it costs more than metronidazole. Randomized controlled trials suggest that tinidazole is equivalent to, or superior to, metronidazole in achieving parasitologic cure and resolution of symptoms [11]. Some strains of *T. vaginalis* can have diminished susceptibility to nitroimidazoles; however, most infections will respond to higher doses of metronidazole or tinidazole. In vitro data and limited clinical investigations support the efficacy of tinidazole when treatment with metronidazole fails [12, 13].

Syphilis remains an important problem because of recent increases in primary and secondary syphilis [3], especially among men who have sex with men (MSM) and because of biological interactions facilitating HIV acquisition and transmission [14]. Long-acting preparations of penicillin remain the treatment of choice for all stages of syphilis. Limited data are available on the management of early syphilis in those with penicillin allergy (ceftriaxone, azithromycin) and on the appropriate dose and duration of these alternative regimens. However, recent reports have described clinical treatment failure in MSM who received azithromycin for early syphilis; treatment failure is associated with a 23S ribosomal RNA mutation that confers macrolide resistance [15]. HIV-infected persons who have early syphilis should be

managed according to standard treatment recommendations; however, there may be an increased risk of neurologic complications and higher rates of treatment failure. No treatment regimens for syphilis have been demonstrated to be more effective in preventing neurosyphilis in HIV-infected persons than the regimens that are recommended for HIV-negative persons [16]. The natural history of treponemal invasion of the CNS in HIV-infected persons is not well defined, but some investigators have suggested that lumbar puncture be considered in persons with syphilis who have a rapid plasma reagin of  $\geq 1:32$  (regardless of stage), especially with concomitant HIV infection with CD4 cell counts  $\leq 350$  cells/mm<sup>3</sup> [17]. Abnormalities of the CSF (pleocytosis or elevated protein levels) are common in early syphilis and among persons with HIV infection; however, there is no evidence to suggest that these abnormalities reliably predict the need for aggressive treatment regimens.

Lymphogranuloma venereum (LGV), caused by *C. trachomatis* serovars L1, L2, and L3, most typically presents as a self-limited genital ulcer, followed by tender inguinal or femoral adenopathy. However, an increasingly recognized presentation has recently been observed in MSM with rectal ulceration, purulent anal discharge, fever, tenesmus, and lower abdominal pain [18]. LGV diagnosis can be challenging and should be based on clinical suspicion, local epidemiology, *C. trachomatis* testing, and the exclusion of other etiologies. Genital and lymph node specimens can be tested for *C. trachomatis*, but nucleic acid amplification tests are not cleared by the Food and Drug Administration for testing rectal specimens, and genotyping (not widely available) is required for differentiating LGV from non-LGV serovars. Chlamydia serologic tests can support the diagnosis in the appropriate clinical context, but LGV test interpretation is not standardized, the tests have not been validated for proctitis presentations, and *C. trachomatis* serovar-

specific serologic tests are not widely available. Because of the current limitations in LGV diagnostic capabilities (lack of rapid, widely available, standardized testing), the clinical management of persons with symptoms suggestive of LGV should include presumptive treatment.

Scabies infestation is a common cause of pruritus and skin rash worldwide. Ivermectin represents a new oral therapeutic option for scabies and may hold particular promise in the treatment of severe infestation or in epidemic situations. Lindane should be used only as an alternative therapy, because of the risk of neurotoxicity and aplastic anemia. No controlled studies for crusted scabies have been conducted, but combination therapy with ivermectin and topical scabicides may prove to be a useful option. Pediculosis pubis is treated with either permethrin cream or pyrethrins; however, increasing rates of drug resistance to these pediculicides may effect their efficacy in the future. Malathion can be used when treatment failure is believed to have occurred because of resistance [19].

An important part of STD treatment is the evaluation and treatment of sex partners. Partner management can be provided directly by the health care provider or with assistance from the health department. The provision of partner services and the specific STDs for which they are offered may vary among providers, agencies, and geographic areas. Expedited partner therapy may be an option for management of heterosexual patients with chlamydia or gonorrhea, in which partners of infected patients are treated without medical evaluation or prevention counseling. More information about expedited partner therapy can be found at the CDC Web site [20]. However, certain operational barriers exist, including the lack of clarity about the legal status of expedited partner therapy in some settings. There is no evidence to support the use of expedited partner therapy in the management of syphilis or among MSM with chlamydia or gonorrhea.

Health care providers can assist in the prevention of STDs through education and counseling of persons at risk, identification of asymptomatic infection, appropriate diagnosis and treatment of infected persons and their sex partners, and pre-exposure vaccination of persons at risk for a vaccine-preventable STD. The publication of national guidelines for the management of STDs provides the clinical guidance necessary to deliver optimal care in both the public and private sectors. STD treatment recommendations will continue to evolve, reflecting advances in basic and clinical research, emerging antimicrobial resistance, and changing sexual and health care behaviors. Utilization of new and more effective treatment regimens, highly sensitive tests for screening for asymptomatic infection, improvements in counseling of patients and their sex partners, and new vaccines for sexually transmitted pathogens are crucial to the achievement of the broader public health goals of improving sexual and reproductive health.

## Acknowledgments

**Supplement sponsorship.** This article was published as part of a supplement entitled "Sexually Transmitted Diseases Treatment Guidelines," sponsored by the Centers for Disease Control and Prevention.

**Potential conflicts of interest.** K.A.W. has research funding from the National Institutes of Health, the Centers for Disease Control and Prevention, Bristol-Myers Squibb, and Tibotec and is a consultant for Abbott and Bristol-Myers Squibb. S.M.B.: no conflicts.

## References

1. Weinstock H, Berman S, Cates W. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. *Perspect Sex Reprod Health* 2004; 36:6–10.
2. Centers for Disease Control and Prevention, Workowski KA, Berman SM. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 2006; 55(RR-11):1–94.
3. Centers for Disease Control and Prevention. Sexually transmitted disease surveillance, 2004. Atlanta, GA: US Department of Health and Human Services, September 2005.
4. US Preventative Services Task Force. Screening for chlamydial infection: recommendations and rationale. *Am J Prev Med* 2001; 20(Suppl 3):90–4.

5. Whittington WL, Kent C, Kissinger P, et al. Determinants of persistent and recurrent *Chlamydia trachomatis* infection in young women: results of a multicenter cohort study. *Sex Transm Dis* **2001**; 28:117–23.
6. Gonococcal Isolate Surveillance Project (GISP). Available at: <http://www.cdc.gov/std/gisp>. Accessed 19 January 2007.
7. Mrazek JM, Handsfield HH, Whittington WL. Predicting chlamydial and gonococcal cervical infection: implications for management of cervicitis. *Obstet Gynecol* **2002**; 100:579–84.
8. Sutton MY, Sternberg M, Zaidi A, St. Louis ME, Markowitz LE. Trends in pelvic inflammatory disease hospital discharges and ambulatory visits, United States, 1985–2001. *Sex Transm Dis* **2005**; 32:778–84.
9. Ness RB, Soper DE, Holley RL, et al. Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease: results from the Pelvic Inflammatory Disease Evaluation and Clinical Health (PEACH) randomized trial. *Am J Obstet Gynecol* **2002**; 186:929–37.
10. Beigi RH, Austin MN, Meyn LA, Krohn MA, Hillier SL. Antimicrobial resistance associated with the treatment of bacterial vaginosis. *Am J Obstet Gynecol* **2004**; 191:1124–9.
11. Forna F, Gulmezoglu AM. Interventions for treating trichomoniasis in women. *Cochrane Database Syst Rev* **2003**; 2:CD000218
12. Crowell AL, Sanders-Lewis KA, Secor WE. In vitro metronidazole and tinidazole activities against metronidazole-resistant strains of *Trichomonas vaginalis*. *Antimicrob Agents Chemother* **2003**; 47:1407–9.
13. Sobel JD, Nyirjesy P, Brown W. Tinidazole therapy for metronidazole-resistant vaginal trichomoniasis. *Clin Infect Dis* **2001**; 33: 1341–6.
14. Fleming DT, Wasserheit JN. From epidemiologic 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.
15. Lukehart SA, Godornes C, Molini BJ, et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med* **2004**; 351:154–8.
16. 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**; 337:307–14.
17. Marra CM, Maxwell CL, Smith SL, et al. Cerebrospinal fluid abnormalities in patients with syphilis: association with clinical and laboratory features. *J Infect Dis* **2004**; 189:369–76.
18. Nieuwenhuis RF, Ossewaarde JM, Gotz HM, et al. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of *Chlamydia trachomatis* serovar I2 proctitis in The Netherlands among men who have sex with men. *Clin Infect Dis* **2004**; 39:996–1003.
19. Chosidow O. Scabies and pediculosis. *Lancet* **2000**; 355:819–26.
20. Centers for Disease Control and Prevention. Expedited partner therapy in the management of sexually transmitted diseases. Available at: <http://www.cdc.gov/std/treatment/EPTFinalReport2006.pdf>. Accessed 20 December 2006.