

Sexually Transmitted Disease (STD) Update: A Review of the CDC 2010 STD Treatment Guidelines and Epidemiologic Trends of Common STDs in Hawai'i

Alan R. Katz MD; Maria Veneranda C. Lee MS; and Glenn M. Wasserman MD

Abstract

The US Centers for Disease Control and Prevention recently updated its recommendations for treating sexually transmitted diseases (STDs). In this review we highlight new treatment recommendations for mitigating the increasing prevalence of antibiotic-resistant *Neisseria gonorrhoeae*, the emergence of azithromycin-resistant *Treponema pallidum*, and treatment options for bacterial vaginosis and venereal warts. We also cover epidemiologic trends for common STDs in Hawai'i.

Introduction

The US Centers for Disease Control and Prevention (CDC) serves as the nation's expert voice on public health and prevention recommendations.¹ Every four years, the CDC convenes a group of professionals with expertise in sexually transmitted diseases (STD). The outcome of this consultation is the publication of updated STD treatment guidelines which are meant to serve healthcare professionals as a source of clinical guidance for the diagnosis and treatment of STDs. The 2010 STD treatment guidelines contain important new information and recommendations.² The purpose of this paper is to highlight the updated recommendations and trends for treatment of common STDs in Hawai'i. Table 1 presents a summary of the recent changes and the rationale for the changes by disease; further discussion of current treatment recommendations and factors relevant to Hawai'i may be found under the respective disease sections of the text.

Gonorrhea

Antibiotic-resistant *Neisseria gonorrhoeae* continues to be a significant public health concern. High-level resistance to penicillin and tetracycline has been recognized since the 1970s.³ Fluoroquinolones, listed as a recommended therapeutic regimen for uncomplicated gonococcal infections in the CDC 2006 STD treatment guidelines,⁴ are now contraindicated due to the rapid spread of resistant isolates, which first appeared in the United States in Hawai'i.⁵ The first *N. gonorrhoeae* isolate in the US with high-level resistance to azithromycin was identified in Hawai'i in May 2011.⁶ Hawai'i was selected as a sentinel site for national gonococcal surveillance as it is recognized as a "port of import" for antimicrobial resistant strains entering the United States.⁷ The CDC currently notes that "third generation cephalosporins remain the sole class of antibiotics available which can be used effectively against *N. gonorrhoeae*."³ Unfortunately, isolates with reduced sensitivity to oral cephalosporins have begun to emerge⁸⁻¹¹ and a small number of isolates with reduced susceptibility to ceftriaxone have also been identified.¹² Three persons in Hawai'i, in 2003, were infected with a strain of multidrug resistant *N. gonorrhoeae*

that demonstrated decreased sensitivity to cefixime.¹¹ This was the first identification of this strain in the United States. Of note, the strain was epidemiologically linked to Japan. In 2009, the first multidrug resistant gonococcal isolate with resistance to ceftriaxone was identified in Japan.¹³ In Hawai'i, of 216 isolates of *N. gonorrhoeae* tested during 2010, 87.0% were susceptible to cefpodoxime (MIC ≤ 0.5 $\mu\text{g/ml}$) and 99.1% were susceptible to azithromycin (MIC ≤ 2.0 $\mu\text{g/ml}$). Ceftriaxone and cefixime were the only antibiotics for which isolates demonstrated 100% susceptibility (Hawai'i Department of Health [HDOH] unpublished data).

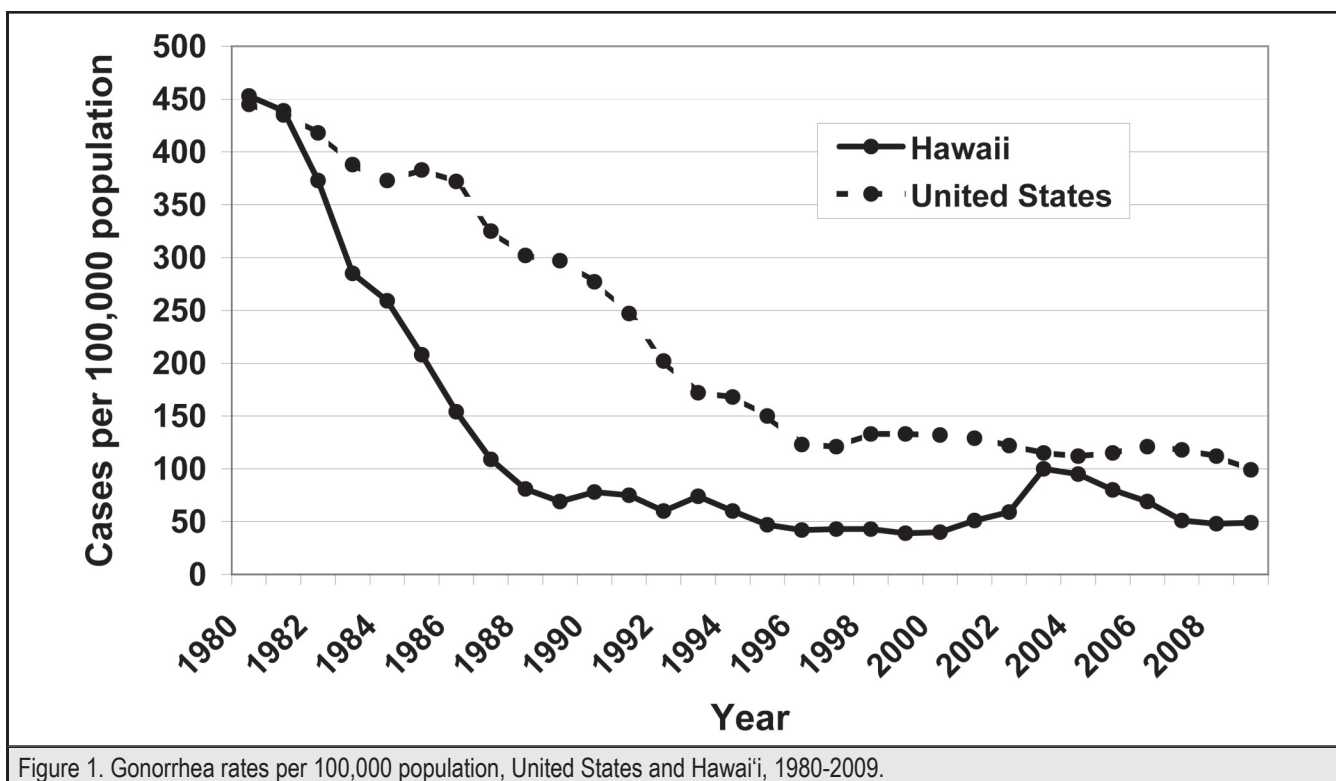
While screening recommendations remain unchanged, gonorrhea screening with culture should be considered for patients who traveled to or who have sex partners with travel histories to countries where antibiotic resistant *N. gonorrhoeae* is present.¹⁴ Increased numbers of antibiotic resistant *N. gonorrhoeae* have also been noted among men who have sex with men (MSM).

In order to mitigate emerging cephalosporin resistance, the CDC 2010 STD treatment guidelines recommend that all cases of gonorrhea (uncomplicated urethral, cervical, anal, and oropharyngeal) be treated with 250 mg ceftriaxone intramuscularly (IM) plus either one gram oral azithromycin or one week of oral doxycycline 100 mg twice a day. This reflects a doubling of the ceftriaxone dose from 125 mg recommended in the 2006 treatment guidelines.⁴ The use of an oral cephalosporin, cefixime (previously listed as an alternative treatment for uncomplicated infections not involving the oropharynx) is discouraged unless injectable ceftriaxone is "not an option."

The CDC 2006 STD treatment guidelines also recommended a two-drug approach (oral or injectable cephalosporin plus azithromycin or doxycycline) for patients diagnosed with gonorrhea in order to cover possible co-infection with *Chlamydia trachomatis*, unless chlamydia infection had been ruled out by nucleic acid amplification testing (NAAT).⁴ In contrast, the CDC 2010 STD treatment guidelines recommend a two-drug approach even if chlamydia has been ruled out.² A multidrug therapeutic approach to address the emergence of antimicrobial resistance is similar to the strategy currently used for the treatment of HIV/AIDS and tuberculosis. In cases where chlamydia has not yet been ruled out, this enables adequate therapeutic coverage for both infections.

In summary, mitigating the emergence of antibiotic resistant gonorrhea is the driving force behind three new gonorrhea treatment recommendations: (1) injectable ceftriaxone should be used rather than oral cefixime; (2) the injectable ceftriaxone dose should be doubled from 125 mg to 250 mg; and (3) one gram oral azithromycin or one week of oral doxycycline 100

Table 1. List of Key Updates in the CDC's 2010 STD Treatment Guidelines		
Disease	Specific Change or Update	Rationale
Gonorrhea	(1) Increase dose of ceftriaxone (to 250 mg); (2) avoid oral cephalosporins unless injectable cephalosporin unavailable; and (3) use of dual therapy (ceftriaxone plus azithromycin or doxycycline) whether or not chlamydia co-infection has been ruled out	To mitigate emergence of antimicrobial resistant <i>N. gonorrhoeae</i>
Syphilis	Do not substitute single dose azithromycin in patients with penicillin allergy	Due to emergence of azithromycin/macrolide resistant <i>T. pallidum</i>
Bacterial Vaginosis	Tinidazole listed as an alternative treatment regimen	Metronidazole is still the first line drug, but tinidazole is now an alternative regimen
Genital Warts	Topical sinecatechin 15% ointment listed as an alternative treatment regimen	An addition to the list of patient applied therapies. Listed as an alternative treatment option
Trichomoniasis	2 new rapid point-of-care tests cleared by the FDA	Provides improved sensitivity over usual form of diagnosis: visualization of motile trichomonads using light microscopy of vaginal secretions



mg twice a day should be administered with IM ceftriaxone whether or not chlamydia infection has been ruled out.¹⁵

The HDOH recommends that *N. gonorrhoeae* cultures, if available, be obtained prior to treatment from persons either treated presumptively or found to be positive for gonorrhea by NAAT. Patients with suspected treatment failures should have specimens obtained for culture and antimicrobial susceptibility testing and should be promptly reported to the HDOH STD/AIDS Prevention Branch. Contact information is provided under the section entitled “Additional resources” at the end of this paper. HDOH is available to assist in medical management of suspected treatment failures and partner management.

Sexual partners of patients with gonorrhea whose last contact

was within 60 days before onset of symptoms or diagnosis should be evaluated and treated. Due to the increased likelihood of reinfection, patients with gonorrhea should be retested three months after treatment.

Gonorrhea rates have been consistently lower in Hawai'i when compared to the country as a whole (Figure 1). This is in part due to an active and widescale culture-based screening program and partner notification activities for gonorrhea cases coordinated through the HDOH. The HDOH Gonorrhea Culture Screening Program, established in 1972, provides free gonorrhea culture-based screening to selected private and public sector providers including community health centers, hospital-based clinics, family planning clinics, and correctional facilities.

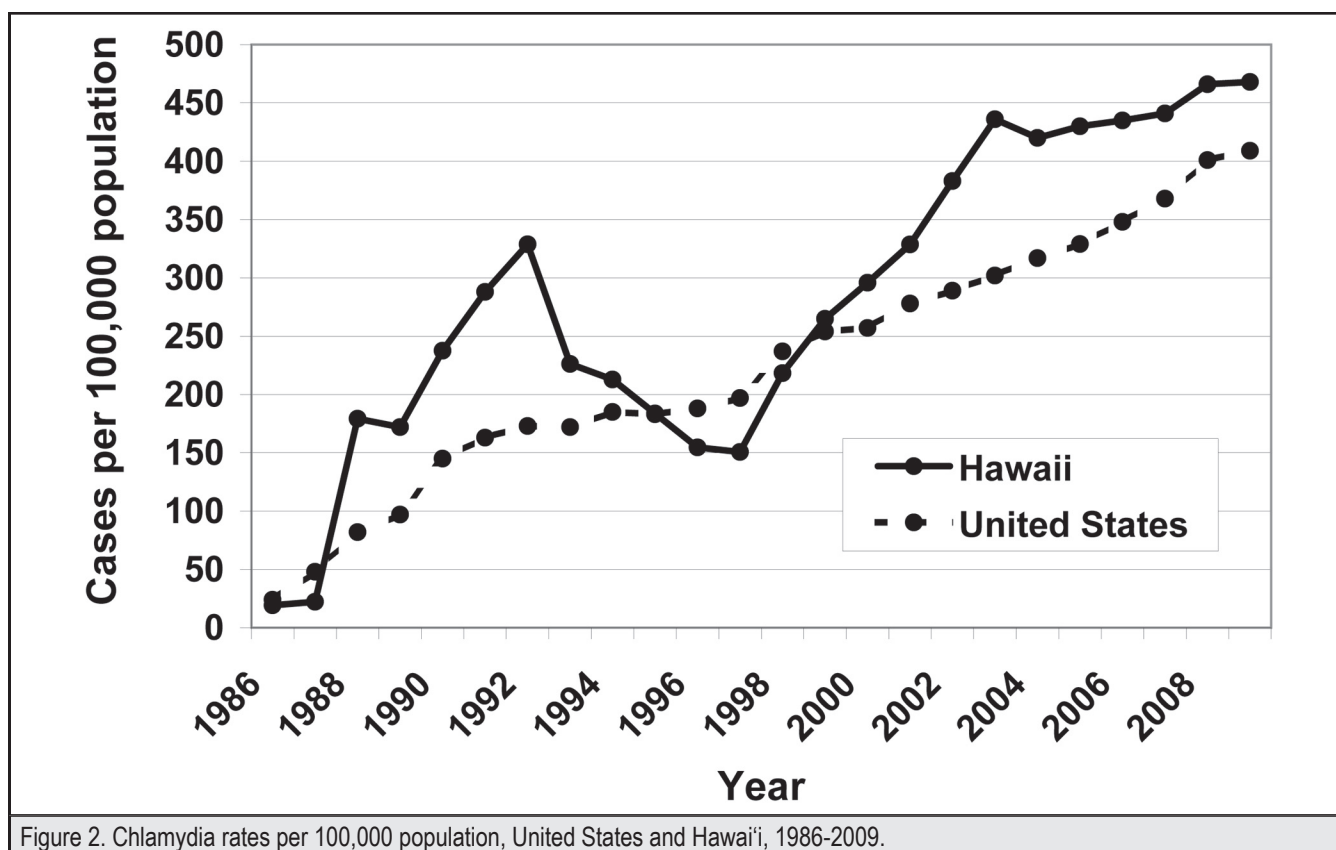


Figure 2. Chlamydia rates per 100,000 population, United States and Hawai'i, 1986-2009.

Chlamydia trachomatis

The 2010 treatment recommendations for *C. trachomatis* remain essentially unchanged: one gram of oral azithromycin or one week of oral doxycycline 100 mg twice a day are the recommended regimens. Screening recommendations are also unchanged. Chlamydia remains the number one reportable infectious disease in both the United States and Hawai'i, and the prevalence is highest among adolescents. Since most infected persons, up to 50% of men and 70% of women, are asymptomatic, detection relies on routine screening. The CDC recommends all sexually active women 25 years of age or younger be screened at least annually for chlamydia. Women 26 years of age and older with risk factors (eg, new or multiple partners) should also be screened annually. According to the latest Healthcare Effectiveness Data and Information Set (HEDIS) report card, Hawai'i had the highest screening rate among states in the United States at 57.8%.¹⁶ A recent survey of physicians in Hawai'i caring for 15-19 year old females was conducted to assess chlamydia screening practices and beliefs and identify potential barriers to screening. Obstetrician-gynecologists, community health center physicians, and physicians aware of reimbursement for screening were more likely to routinely screen these younger patients. Physicians in private practice settings and those who felt only "high risk" adolescents should be targeted for screening were less likely to routinely screen.¹⁷

Reported chlamydia rates in Hawai'i have been consistently higher than that of the United States (Figure 2). As most chla-

mydia cases are under 25 years of age and asymptomatic, case identification is dependent on screening. Hawai'i has been and remains at the forefront nationally with respect to chlamydia screening activity. Not only was Hawai'i one of the first states to initiate a chlamydia screening program,¹⁸ but as noted previously, Hawai'i has maintained an active screening program with the highest screening rate nationally. The HDOH Hawai'i Chlamydia Screening Program partners with private and public sector providers including community health centers, family planning providers, hospital-based clinics, college-based clinics, correctional facilities, and employer health care plans, to provide screening for women as part of the CDC Infertility Prevention Project.

Sexual partners of patients with chlamydia whose last contact was within 60 days preceding symptom onset or diagnosis should be referred for evaluation and treatment. Due to the increased likelihood of reinfection, it is recommended that patients with chlamydia be retested three months after treatment.

Syphilis

Although penicillin G, administered parenterally, is the preferred drug for treatment of all stages of syphilis, the CDC 2006 and 2010 STD treatment guidelines note that doxycycline 100 mg given orally twice a day for 14 days or tetracycline 500 mg given orally four times a day for 14 days could be considered as treatment options for primary or secondary syphilis in cases of penicillin allergy. Also noted in the 2006 guidelines was the

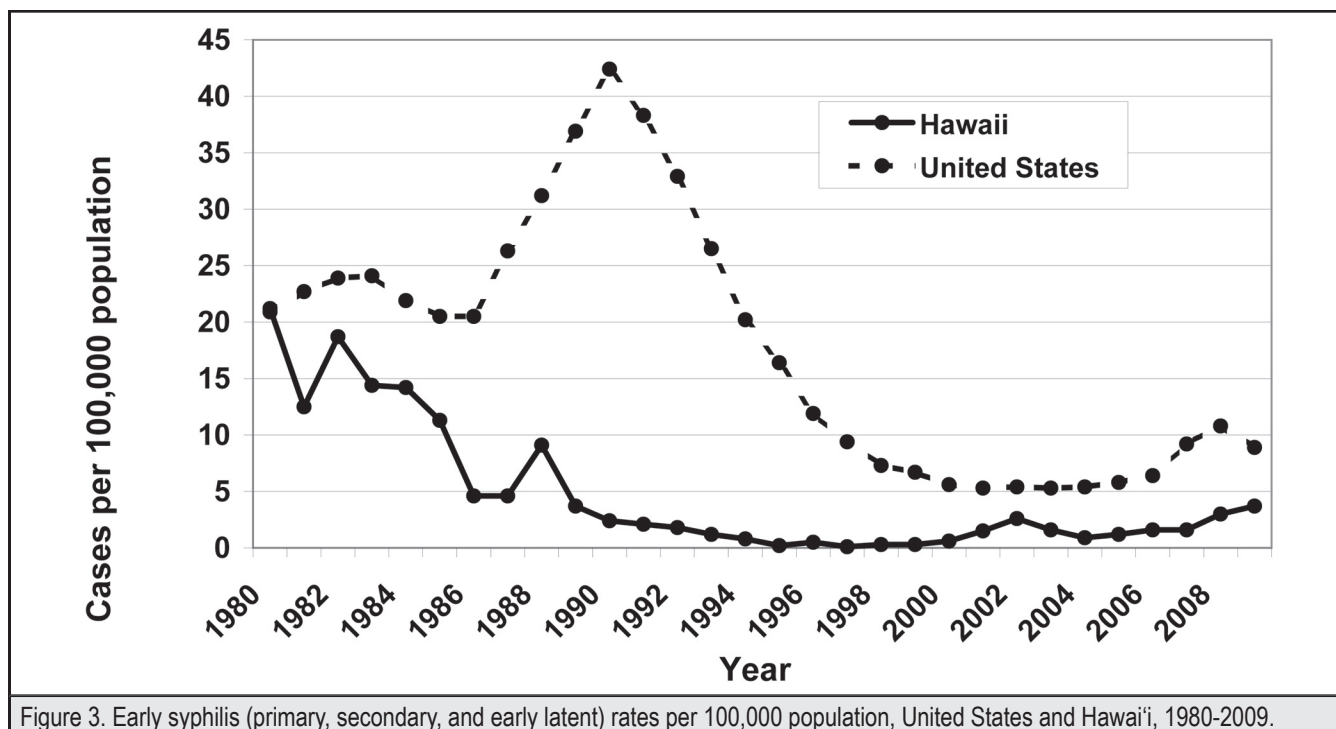


Figure 3. Early syphilis (primary, secondary, and early latent) rates per 100,000 population, United States and Hawai'i, 1980-2009.

use of a single two gm oral azithromycin dose as a treatment option for primary or secondary syphilis in cases of penicillin allergy. The updated 2010 guidelines warn against the use of single dose azithromycin due to the emergence of azithromycin-resistant strains of *T. pallidum*.²

Persons sexually exposed within 90 days to a partner diagnosed with primary, secondary, or early latent syphilis might be infected even if their serological test results are negative, hence the CDC recommends that they be evaluated clinically and serologically for syphilis, but that they be treated presumptively regardless of their test results.

Patients with syphilis should also be routinely tested for HIV infection as there is a well recognized risk of co-infection. Most syphilis cases in the United States and Hawai'i are in men, and Men who have Sex with Men (MSM) are over-represented for both infections. In Hawai'i, between 2001 and 2010, 87% of primary and secondary syphilis cases occurred in men, and 74% of male cases were MSM. In addition, 34% of MSM who were diagnosed with primary or secondary syphilis self-disclosed that they were also HIV-infected (HDOH unpublished data).

Syphilis rates in Hawai'i have consistently fallen below those reported nationally (Figure 3). Unfortunately rates in Hawai'i have gradually increased over the past decade. This has involved both MSM and heterosexuals, including an outbreak in 2007 among heterosexual Micronesians on Oahu.¹⁹

There has been a recent increase in the proportion of females diagnosed with primary and secondary syphilis in Hawai'i. From 2001-2007, women accounted for only 4% of all reported cases; from 2008-2010, approximately 20% of reported cases were women (HDOH unpublished data).

Bacterial Vaginosis

First line recommended treatment regimens remain the same: metronidazole, 500 mg twice a day given orally for seven days or metronidazole gel 0.75%, one applicatorful intravaginally at bedtime for seven days or clindamycin cream 2%, one applicatorful intravaginally at bedtime for seven days. A new alternative regimen is tinidazole two grams orally once daily for two days or tinidazole one gram orally once daily for five days.² Routine treatment of sexual partners is not recommended.

Trichomoniasis

The US Food and Drug Administration (FDA) recently cleared two rapid point-of-care tests for trichomoniasis: OSOM Trichomonas Rapid Test and Affirm VP III. The diagnosis is usually made by microscopic examination of a vaginal secretion "wet prep," but the reported sensitivity of this method is only 60%-70%. Point-of-care tests are more sensitive than the wet prep, but false positives may occur. Culture is also a possible diagnostic choice. FDA-cleared NAATs for gonorrhea and chlamydia have been modified for *T. vaginalis* detection and have excellent sensitivity and specificity.²⁰⁻²² The recommended treatment regimens remain unchanged at either two grams of oral metronidazole or tinidazole in a single dose. Sex partners of patients infected with *T. vaginalis* should also be treated with the same regimen.

Venereal Warts

In addition to the previously listed provider-administered therapies (cryotherapy, podophyllin resin, or trichloacetic acid) and patient-applied therapies (podofilox solution or gel

and imiquimod cream), a new patient-applied therapy has been added to the list of recommended regimens: sinecatechin 15% ointment, applied three times daily for up to 16 weeks. Sinecatechin, whose active ingredient, catechin, is extracted from green tea, is not noted to be safer or more effective, but is another option.²

The HPV vaccine is currently recommended for females ages 11-12 years (with catch up recommended for 13-26 year olds who have not been vaccinated). Two vaccines are currently cleared by the FDA: Gardasil (quadrivalent) and Cervarix (bivalent). Recommendations were extended to males on 25 October 2011 and are specifically for the quadrivalent vaccine. Males ages 11-12 years should be routinely vaccinated (with catch up recommended for 13-21 year olds who have not been vaccinated). Males aged 22-26 years may also be vaccinated.²³

General Comments

Factors identified by the CDC which increase one's risk for STD include having a past history of an STD, having unprotected sex, and having multiple partners or a partner who has multiple partners. The CDC also advises that, "patients seeking treatment or screening for a particular STD should be evaluated for all common STDs."²²

Expedited Partner Therapy

Expedited Partner Therapy (EPT) is treating partners of patients by providing the patient with either a prescription or medication to take to his/her partner without having a healthcare provider first examining the partner. The CDC has concluded that EPT is a useful option for partners of heterosexual men or women with gonorrhea or chlamydia. This is especially true when a partner is unlikely to seek evaluation and treatment on his/her own. No recommendations are in place for MSM. As of 10 August 2011, EPT is permissible in 30 states, potentially allowable in 13 states, and prohibited in 7 states.^{2,24} EPT is currently not legally sanctioned in Hawai'i, but is "potentially allowable" under Hawai'i Revised Statutes chapter 328, section 328-16. The American College of Obstetricians and Gynecologists (ACOG) recently endorsed EPT as a strategy to prevent STD re-infection, and in a recent news release stated: "The College encourages ob-gyns to push for legalization of expedited partner therapy in those states and jurisdictions where it's illegal or where the legal status of EPT is unclear or ambiguous."²⁵

Hawai'i State STD Reporting Requirements

Gonorrhea, chlamydia, syphilis, HIV/AIDS, pelvic inflammatory disease, and chancroid (a genital ulcerative STD which has, to date, not been identified in Hawai'i) are all notifiable diseases under Hawai'i Administrative Rules, Title 11, Chapter 156. The statute requires a written or phone report by the diagnosing clinician to the HDOH STD/AIDS Prevention Branch within three days of diagnosis. Disease intervention specialist services are available through HDOH to help identify and treat locatable sexual partners. This strives to decrease the probability of reinfection of the "index case" and further transmission to others.

Reporting Sources

Chlamydia and gonorrhea are the most common notifiable sexually transmitted diseases in Hawai'i and nationally. Most cases in Hawai'i are reported from private sector providers. In 2010, 60% of gonorrhea cases were reported from the private sector, 20% from military providers, and 20% from the HDOH Diamond Head STD Clinic.²⁶ In 2010, the HDOH Gonorrhea Culture Screening Program screened 13,275 persons and identified 216 cases. This accounted for 28% of all gonorrhea cases reported. Seventy-one percent of chlamydia cases were reported by private sector providers, 21% from the military, and 8% from the HDOH Diamond Head STD Clinic.²⁶ In 2010, the HDOH Hawai'i Chlamydia Screening Program screened 17,353 women and identified 1,118 cases. This accounted for 26% of all chlamydia cases identified in females and 19% of total cases reported.

Additional Resources

The HDOH STD/AIDS Prevention Branch maintains an updated website with links to the 2010 CDC STD treatment guidelines, STD screening recommendations, medical advisories, relevant peer reviewed journal articles, and information on the epidemiology of STDs in Hawai'i. The URL address is: <http://hawaii.gov/health/healthy-lifestyles/std-aids/index.html>. The HDOH operates a free, first-come-first-served STD clinic/HIV testing site located at the Diamond Head Health Center, 3627 Kilauea Avenue, Room 305, Honolulu, HI 96816, phone: 808-733-9281, fax: 808-733-9291. Clinic hours are Monday through Friday, 11 am to 4 pm. This is the same address for clinicians to submit written, phone, or fax reports for notifiable STDs and is the HDOH resource if one has STD/HIV questions, consultation requests, or desires additional information. The CDC also maintains an excellent website for STD related information. This includes national surveillance information, updated screening and treatment recommendations, and downloadable, simply written, patient information fact sheets for individual STDs. The URL address is: <http://www.cdc.gov/std>. Additional information may also be accessed through the California STD/HIV Prevention Training Center (CPTC). CPTC is part of a national CDC-funded training network "designed to enhance the STD/HIV knowledge and skills of medical, health, and community professionals." Their URL address is: <http://www.stdhivtraining.org>.

Disclosure Statement

The authors have no financial relationships with any of the products discussed. In addition, none of the authors identify any potential conflicts of interest.

Authors' Affiliation:

- Department of Public Health Sciences, John A. Burns School of Medicine, University of Hawai'i (ARK)
- STD/AIDS Prevention Branch, Communicable Disease Division, Hawai'i State Department of Health (ARK, MVCL)
- Communicable Disease Division, Hawai'i State Department of Health (GMW)

Correspondence to:

Alan R. Katz MD; Department of Public Health Sciences, Biomedical Sciences Building, Room D104M, 1960 East-West Road, Honolulu, HI 96822;
Ph: (808) 956-5741; Email: katz@hawaii.edu

References

- Centers for Disease Control and Prevention. CDC vision for the 21st century. Available at URL: <http://www.cdc.gov/about/organization/mission.htm>. Accessed 14 October 2011.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010;59(RR-12).
- Centers for Disease Control and Prevention. Consultation meeting on cephalosporin-resistant gonorrhea outbreak response plan. 12-15 September 2009. Available at URL: <http://www.cdc.gov/std/Gonorrhea/arg/CephOutbreakResponsePlan.pdf>. Accessed 14 October 2011.
- Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2006. *MMWR Recomm Rep* 2006;55(RR-11):42-9.
- Centers for Disease Control and Prevention. Update to CDC's sexually transmitted disease treatment guidelines, 2006: fluoroquinolones no longer recommended for treatment of gonococcal infections. *MMWR Morb Mortal Wkly Rep* 2007;56:332-6.
- Centers for Disease Control and Prevention. Dear colleague letter: azithromycin resistance in Hawaii. 24 May 2011. Available at URL: <http://www.cdc.gov/std/gonorrhea/DCL-Azithro-GC-May-24-2011.pdf>. Accessed 14 October 2011.
- Centers for Disease Control and Prevention. Sentinel surveillance for antimicrobial resistance in *Neisseria gonorrhoeae*—United States, 1988-1991. *MMWR Surveill Summ* 1993;42(SS-3):29-39.
- Lo JY, Ho KM, Leung AO, et al. Cefixime resistance and treatment failure of *Neisseria gonorrhoeae* infection. *Antimicrob Agents Chemother* 2008;52:3564-7.
- Yokoi S, Deguchi T, Ozawa T, et al. Threat to cefixime treatment for gonorrhea. *Emerg Infect Dis* 2007;13:1275-7.
- Muratani T, Akasaka S, Kobayashi T, et al. Outbreak of cefazopran (penicillin, oral cepheps, and aztreonam)-resistant *Neisseria gonorrhoeae* in Japan. *Antimicrob Agents Chemother* 2001;45:3603-6.
- Wang SA, Lee MV, O'Connor N, et al. Multidrug-resistant *Neisseria gonorrhoeae* with decreased susceptibility to cefixime-Hawaii, 2001. *Clin Infect Dis* 2003;37:849-52.
- Tapsall J, Read P, Carmody C, et al. Two cases of failed ceftriaxone treatment in pharyngeal gonorrhoea verified by molecular microbiological methods. *J Med Microbiol* 2009;58(Pt 5):683-7.
- Ohnishi M, Saika T, Hoshina S, et al. Ceftriaxone-resistant *Neisseria gonorrhoeae*, Japan [letter]. *Emerg Infect Dis* 2011;17:148-9.
- World Health Organization. Emergence of multi-drug resistant *Neisseria gonorrhoeae*—threat of global rise in untreatable sexually transmitted infections. 11 April 2011. Available at URL: http://whqlibdoc.who.int/hq/2011/WHO_RHR_11.14_eng.pdf. Accessed 14 October 2011.
- Katz AR. STDs: drug resistance demands dual therapy [letter]. *J Fam Pract* 2011;60:320.
- Centers for Disease Control and Prevention. Chlamydia screening among sexually active young female enrollees of health plans—United States, 2000-2007. *MMWR Morb Mortal Wkly Rep* 2009;58:362-5.
- McGrath CM, Katz AR, Lee MVC, Rochat RW. Chlamydia screening of adolescent females: a survey of providers in Hawaii. *J Community Health* 2011;36:274-80.
- Katz AR. The Hawaii chlamydia network project: a successful program incorporating close intra-agency cooperation. *Am J Public Health* 1989;79:505-7.
- Katz AR, Cadorna AM, Lee MVC, Komeya A, Kiaha M, Ohye RG. Investigation of a cluster of syphilis, gonorrhea, and chlamydia cases among heterosexual Micronesians living on Oahu. *J Community Health* 2009;34:357-60.
- Van Der PB, Kraft CS, Williams JA. Use of an adaption of a commercially available PCR assay aimed at diagnosis of chlamydia and gonorrhea to detect *Trichomonas vaginalis* in urogenital specimens. *J Clin Microbiol* 2006;44:366-73.
- Hardick A, Hardick J, Wood BJ, et al. Comparison between the GenProbe transcription-mediated amplification *Trichomonas vaginalis* research assay and real-time PCR for *Trichomonas vaginalis* detection using a Roche LightCycler instrument with female self-obtained vaginal swab samples and male urine samples. *J Clin Microbiol* 2006;44:4197-9.
- Nye MB, Schwelbe JR, Body BA. Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and polymerase chain reaction for diagnosis of trichomoniasis in men and women. *Am J Obstet Gynecol* 2009;200:188-97.
- Centers for Disease Control and Prevention. Recommendations on the use of quadrivalent human papillomavirus vaccine in males—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep* 2011;60:1705-8.
- Centers for Disease Control and Prevention. Expedited partner therapy. Available at URL: <http://www.cdc.gov/std/ept/legal/default.htm>. Accessed 14 October 2011.
- American College of Obstetricians and Gynecologists. Expedited Partner Therapy Recommended to Prevent STI Reinfection. Press Release. 22 August 2011. Available at URL: http://www.acog.org/from_home/publications/press_releases/nr08-22-11-2.cfm. Accessed 14 October 2011.
- Hawaii State Department of Health. STD/AIDS Prevention Branch. Epidemiology: data and statistics. Available at URL: <http://hawaii.gov/health/healthy-lifestyles/std-aids/data-statistics/index.html#stds>. Accessed 14 October 2011.