



eLITERATURE REVIEW

eInfections Review

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eInfections Review: VOLUME 2, NUMBER 11

Recent Changes in Sexually Transmitted Infections

In this Issue...

Sexually transmitted infections (STIs) remain highly prevalent and are associated with significant morbidity worldwide. The majority are asymptomatic, and recent data suggest that a significant number are extragenital. Furthermore, the epidemiology and diagnostic approach to the treatment of some of these infections are in a state of flux; these changes will have a significant impact on patient management.

In this issue, we examine the clinical and public health impact of extragenital STIs, highlighting increasing antimicrobial resistance in *Neisseria gonorrhoeae*, the evolving epidemiology of anogenital herpes virus infections, and the changing algorithm in syphilis testing. Understanding the impact of these changes will allow us to better diagnose and treat patients with STIs.



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Length of Activity

1 hour

Release Date

September 8, 2010

Expiration Date

September 7, 2012

Next Issue

October 5, 2010

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Describe issues related to the emergence of broad, multiclass antimicrobial resistance in *Neisseria gonorrhoeae*.
- Identify risk factors for and explain the importance of detecting and treating extragenital sexually transmitted infections.
- Discuss the changing epidemiology of genital herpes simplex virus infections and the implications associated with a changing approach to syphilis testing.

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- **Paul G. Auwaerter, MD** – has disclosed that he has served as a consultant Adamas Pharmaceuticals, LifeCell, Schering-Plough, and Wyeth. He has disclosed that he is a stock shareholder of Johnson & Johnson, Merck and Pfizer.
- **John G. Bartlett, MD** – has disclosed that he has served as a consultant for Salient.
- **Sara E. Cosgrove, MD, MS** – has disclosed that she has received grants or research support from Cubist, AdvanDX, and Astellas, and served as a consultant for Theravance/Astellas, Merck, and Forest.

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Guest Faculty Disclosures

Khalil G. Ghanem, MD, PhD has disclosed he has no relevant financial relationships.

Unlabeled/Unapproved Uses

The author has indicated that there will be reference to unlabeled/unapproved use of azithromycin to treat gonorrhea and nucleic acid amplification tests (NAATs) to test extragenital sites in this presentation.

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Drug resistance in *Neisseria gonorrhoeae* continues to increase at an alarming rate. Resistance emerged within months after the introduction of penicillin in the 1940s. Since then, penicillins, tetracyclines, and fluoroquinolones can no longer be used to treat gonococcal infections. Currently, the only first-line agents recommended by the Centers for Disease Control and Prevention (CDC) for the treatment of gonococcal infections are the extended-spectrum cephalosporins.¹ A single 125mg dose of intramuscular ceftriaxone is the preferred treatment regimen for uncomplicated anogenital gonorrhea; the CDC is considering increasing that dose to 250mg in an attempt to mitigate the development of drug resistance and overcome an increasing trend in the minimum inhibitory concentrations (MICs) of cephalosporins. In patients with a penicillin allergy, the only alternative recommendation is intramuscular spectinomycin, which is currently not available in the United States. In practice, the only available alternative agent in this country is a single 2g oral dose of azithromycin. The gastrointestinal side effects of high-dose azithromycin are not insignificant, however, and in geographic locales that have routinely used azithromycin, high-level drug resistance has emerged.² In the United States, <1% of *N. gonorrhoeae* isolates have decreased susceptibility to azithromycin, and there have been no recent reports of azithromycin- or cephalosporin-resistant strains. The studies by Monfort and colleagues³ and de Vries and associates⁴ (reviewed herein), conducted in France and the Netherlands, respectively, highlight a troublesome, yet expected, trend: the emergence in Western Europe of *N. gonorrhoeae* strains with decreased susceptibility to cephalosporins. These findings come only months after discontinuation of the routine use of fluoroquinolones for treating gonorrhea in those regions. They follow a more ominous report of high-level cephalosporin resistance leading to clinical treatment failures in the Far East.⁵

The vast majority of genital and extragenital STIs are asymptomatic. *N. gonorrhoeae* and *Chlamydia trachomatis* also infect the rectum and pharynx after unprotected exposures. The CDC recommends screening at-risk men who have sex with men (MSM) at least annually for urethral and rectal gonorrhea and chlamydia and for pharyngeal gonorrhea, but the adoption of this recommendation has been variable.⁶ Clinicians are uncertain about the appropriate approach to use to test for extragenital STIs. Nucleic acid amplification tests (NAATs) have been approved by the US Food and Drug Administration (FDA) and are the gold standard for detecting genital gonococcal and chlamydia infections, but none has been FDA-cleared for extragenital testing. Lack of FDA approval, however, does not mean that NAATs cannot be used to identify extragenital infections. After conducting in-house validation studies, most large laboratories are providing extragenital NAATs. Clinicians should contact their laboratory to determine if such testing is available. The studies by Bernstein and coworkers⁷ and Jin and colleagues⁸ (reviewed in this issue) highlight the clinical and public health importance of extragenital STIs. These authors demonstrate that pharyngeal gonorrhea and chlamydia may be transmitted to a partner's urethra after unprotected fellatio. They also describe a strong association between rectal gonorrhea and HIV seroconversions. Asking about high-risk exposures (rather than symptoms) at genital and extragenital sites will help ensure that STIs do not go undetected.

Anogenital herpes infections have been associated predominantly with herpes simplex virus (HSV) type 2. HSV-1 is also associated with anogenital outbreaks. Although primary infection with these viruses is quite similar, HSV-1 recurrences tend to be less frequent and less severe.⁹ Thus, knowing which virus is responsible for a particular clinical outbreak may help clinicians provide useful counseling information to patients. The study by Ryder and collaborators¹⁰ (discussed herein) highlights the changing epidemiology of HSV infections: HSV-1 is now becoming a more common cause of primary anogenital herpes infections, particularly among young women and young MSM. Infection with HSV-1, however, does not prevent subsequent infection with HSV-2.

Finally, testing for syphilis has been fairly consistent and homogeneous across the United States: A nontreponemal-specific test (e.g., rapid plasma reagin [RPR]) is obtained first and followed, if positive, by a confirmatory treponemal test. The serum RPR is an inexpensive and sensitive test, which also provides titers that can be followed over time. The natural history of the serum RPR titer is to decline, and in a majority of adequately treated patients, it will usually serorevert to negative several years after appropriate therapy.¹¹ The RPR may also revert to negative in untreated patients years after an initial



infection. A CDC¹² report (summarized in this issue) describes a reversal in the typical testing algorithm by some laboratories, whereby a treponemal-specific test is used as the initial screening test followed, if positive, by the serum RPR. This has led to a significant number of serodiscordant results. Knowing how to interpret these results will ensure that infected patients are appropriately managed.

Several areas of STI epidemiology, testing, and treatment are actively changing. In this issue, we highlight some of these recent trends. This information should translate into practical strategies for enhancing the prevention, diagnosis, and treatment of STIs.

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EMERGING ANTIMICROBIAL RESISTANCE IN NEISSERIA GONORRHOEAE

Monfort L, Caro V, Devaux Z, Delannoy AS, Brisse S, Sednaoui P. **First *Neisseria gonorrhoeae* genotyping analysis in France: Identification of a strain cluster with reduced susceptibility to ceftriaxone**. *J Clin Microbiol*. 2009;47(11):3540-3545.

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De Vries HJ, van der Helm JJ, Schim van der Loeff MF, van Dam AP. **Multidrug-resistant *Neisseria gonorrhoeae* with reduced cefotaxime susceptibility is increasingly common in men who have sex with men, Amsterdam, the Netherlands**. *Euro Surveill*. 2009;14(37):1-6

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Since 2007, the CDC has recommended against fluoroquinolones for treating gonococcal infections; extended-spectrum cephalosporins the only first-line agents currently recommended. The recommended second-line agent, spectinomycin, is no longer available in the United States. Gonococcal resistance to cephalosporins has now been reported in the Far East.¹ The goal of the studies by Monfort and coworkers and de Vries and associates was to describe the epidemiology of drug resistance among strains of *N. gonorrhoeae* circulating in France and the Netherlands, respectively.

Monfort and collaborators selected representative isolates of *N. gonorrhoeae* collected between January 2006 and June 2006 by laboratories participating in a French national surveillance network. The choice of isolates was based on the phenotypic analysis of strains and the population from which these strains were isolated. In the study by de Vries and colleagues, the investigators used all gonococcal strains with reported antibiotic susceptibility information collected from an STI outpatient clinic in Amsterdam, The Netherlands, between October 2006 and December 2008. In both the French and Dutch studies, swabs were cultured on routine media in a carbon dioxide-enriched environment, and antibiotic susceptibility was determined using the disk diffusion and E-test methods, respectively.

Monfort reported on the antibiotic susceptibility from 96 of 295 collected strains. The majority of the strains (n=52) had intermediate and high-level resistance to fluoroquinolones. A total of 33 strains had reduced susceptibility to ceftriaxone, with reported minimum inhibitory concentration (MIC) values ranging from 0.012 to 0.032 µg/mL. All strains were susceptible to spectinomycin and macrolides. There was no apparent association between observed resistance and behavioral or geographic parameters. In the de Vries analysis, the authors reported on 1596 patients with available MIC data. They identified 102 patients with >1 strain that demonstrated reduced susceptibility to cefotaxime (MIC >0.125 µg/mL). Of these strains, 30.3% were also resistant to penicillin, tetracycline, and fluoroquinolones. In multivariate analysis, the only risk factor for being infected with a strain that demonstrated reduced susceptibility to cephalosporins was being an MSM.

These 2 European studies, which were conducted shortly after fluoroquinolones were no longer used to treat gonorrhea in France and the Netherlands, demonstrate a very alarming trend for reduced susceptibility of gonococcal isolates to cephalosporins. Such a trend mirrors the emergence of fluoroquinolone resistance and its worldwide spread (e.g., beginning in the Far East, moving west, and initially affecting MSM). Of interest, clinicians in the Netherlands use 500 mg of intramuscular ceftriaxone to treat uncomplicated gonococcal infections, a much higher dose than the one currently recommended in the United States. Despite this high dose, MICs of cephalosporins have increased, and they have done so rapidly. Although neither of these studies reported clinical failures, it is only a matter of time before cephalosporins will no longer be effective for the treatment of gonococcal infections. It is more than likely that the future of gonococcal treatment will involve the use of combination antimicrobial therapy.

Commentary References

1. Lo JY, Ho KM, Leung AO, et al. [Ceftibuten resistance and treatment failure of Neisseria gonorrhoeae infection](#). *Antimicrob Agents Chemother*. 2008;52(10):3564-3567.

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CLINICAL AND PUBLIC HEALTH IMPLICATIONS OF EXTRAGENITAL SEXUALLY TRANSMITTED INFECTIONS

Bernstein KT, Stephens SC, Barry PM, et al. **Chlamydia trachomatis and Neisseria gonorrhoeae transmission from the oropharynx to the urethra among men who have sex with men**. *Clin Infect Dis*. 2009;49(12):1793-1797.

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Like genital STIs, the majority of extragenital STIs are asymptomatic. Unless a clinician asks about exposure, infections at these sites are not likely to be detected. Data on the clinical and public health implications of extragenital infections are limited. In the first study reviewed, Bernstein and associates attempt to better define the public health implications of transmitting oropharyngeal infections with *N. gonorrhoeae* and *C. trachomatis*. In the second study, Jin and colleagues demonstrate the impact of anal STIs on the risk for HIV seroconversion.

Bernstein and collaborators assessed *N. gonorrhoeae* and *C. trachomatis* urethral positivity among all MSM who visited a San Francisco, California, sexually transmitted disease clinic in 2007 and reported that their only urethral exposure in the prior 3 months had been receptive fellatio. NAATs were used to detect *N. gonorrhoeae* and *C. trachomatis* from urine. In the study by Jin and coworkers, the researchers assessed the impact of rectal STIs on the probability of seroconversion among a cohort of HIV-negative MSM in Sydney, Australia, who were enrolled between 2001 and 2004 and were followed prospectively. Participants were tested annually for HIV, anal and urethral gonorrhea, and chlamydia (using NAATs); herpes simplex viruses 1 and 2 (using serologic glycoprotein G-based enzyme immunoassay [EIA] tests); and syphilis. Self-reports of genital and anal warts were also documented.

In the San Francisco study, among 5715 visits by MSM, 397 men reported that their only urethral exposure in the preceding 3 months had been receptive fellatio; 99% reported not using a condom. Of those, 4.1% (95% confidence interval [CI], 2.3% to 6.5%) and 4.8% (95% CI, 2.9% to 7.4%) were diagnosed with *N. gonorrhoeae* and *C. trachomatis*, respectively. HIV-infected MSM were more likely to be diagnosed with these urethral infections than were HIV-uninfected MSM. In the Australian study, 1427 HIV-uninfected men were followed prospectively for a median of 3.9 years. In all, 53 HIV seroconversions were identified. After adjusting for known behavioral and biological risk factors, a diagnosis of anal gonorrhea (hazard ratio [HR]=7.12; 95% CI, 2.05 to 24.75) and an interval self-report of anal genital warts (HR=3.63; 95% CI, 1.62 to 8.14) were both independently associated with HIV seroconversion.

Both studies are limited by the potential for behavioral confounding, and both were conducted among high-risk MSM populations. The CDC recommends screening at-risk MSM at least annually for urethral and rectal gonorrhea and chlamydia, and also for pharyngeal gonorrhea. Although not FDA approved for that purpose, most large laboratories offer NAATs of specimens obtained from these sites. Of note, other studies have demonstrated high rates of extragenital STIs in predominantly heterosexual populations.^{1,2} All of these studies highlight the public health and clinical importance of aggressively screening for and treating extragenital STIs.

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THE CHANGING EPIDEMIOLOGY OF GENITAL HERPES SIMPLEX VIRUS INFECTIONS

Ryder N, Jin F, McNulty AM, Grulich AE, Donovan B. **Increasing role of herpes simplex virus type 1 in first-episode anogenital herpes in heterosexual women and younger men who have sex with men, 1992-2006.** *Sex Transm Infect.* 2009;85(6):416-419.

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HSV is one of the most prevalent STIs in the world. Since 1976, the CDC has monitored HSV-2 seroprevalence in the United States through the National Health and Nutrition Examination Survey. In the 2003 to 2008 survey, HSV-2 seroprevalence was 16.2% and was highest among women (20.9%) and non-Hispanic blacks (39.2%).¹ Although HSV-2 is classically associated with genital herpes, epidemiologic data suggest that HSV-1 is not an infrequent cause of genital herpes. Ryder and colleagues describe the contribution of HSV-1 to all first episodes of symptomatic anogenital herpes in Australia.

The study was conducted at the Sydney Sexual Health Centre, a free public inner-city clinic in Australia. All first-episode anogenital herpes cases identified between 1992 and 2006 were included in the analysis. The diagnosis of HSV was based on cell culture results until 2004 and a validated in-house polymerase chain reaction assay thereafter. Associations with the overall proportion of HSV-1 infections were determined for demographic and clinical parameters.

A total of 4440 clinically defined first episodes of anogenital herpes were reported, with 1845 microbiologically confirmed as HSV. Of those, 35% were HSV-1. The overall proportion from HSV-1 increased from 29% in 1992 to 1994 to 42% in 2004 to 2006. This increase was driven mainly by an increased number of cases among heterosexual women. MSM were more likely than heterosexual men to have a first anogenital episode from HSV-1 (odds ratio = 2.89; 95% CI, 2.15 to 3.87); cases among MSM increased from 6.5% in 1992 to 1994 to 21.4% in 2004 to 2006. In addition, first anogenital cases of HSV-1 were more likely to occur among younger patients, independent of the time period assessed.

The study has several limitations. Only symptomatic anogenital cases were included. A significant proportion of HSV cases are asymptomatic, and data suggest that anogenital HSV-1 is more likely to be asymptomatic than HSV-2. Thus, this study may have underestimated the proportion of HSV cases attributable to HSV-1. The majority of suspected herpes cases in this study remained microbiologically unconfirmed. Since the sensitivity of cell culture is relatively low, this is not surprising. Serologic testing might have helped clarify the epidemiology in the microbiologically unconfirmed patients, but serum was not available for testing. These data confirm smaller studies conducted in the United States and abroad that suggest HSV-1 is a significant cause of anogenital herpes in both men and women.^{2,3} Knowing the HSV serotype is important for clinical prognostication: Compared with patients with HSV-2 infection, those with HSV-1 infection tend to have fewer and less severe recurrences.

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In the United States, serologic testing for syphilis consists of an initial nontreponemal test (usually, the RPR), followed, if positive, by a treponemal-specific test (e.g., fluorescent treponemal antibody absorption test or several treponemal EIA tests). The reason for beginning with a nontreponemal test is cost. The RPR is a relatively inexpensive and sensitive screening test, whereas the treponemal-specific tests are more costly and time-consuming. The recent development of EIAs that are less costly and can be automated has led several large laboratories to reverse the classic algorithm and begin using a treponemal-specific EIA as a screening test, followed, if positive, by the RPR. The goal of this MMWR study was to describe the results of such an algorithm shift in New York City.

Between October 2005 and December 2006, the CDC reviewed the results of a convenience sample of syphilis serologic tests that were conducted by 4 laboratories in New York City. All of the laboratories used an algorithm that consisted of an initial treponemal-specific EIA, followed, if positive, by the RPR. At 2 of the 4 laboratories, samples that were reactive by EIA but nonreactive by RPR were retested using a different treponemal-specific test (the *Treponema pallidum* particle agglutination).

Of the 116,822 specimens included in the convenience sample, 6587 (6%) were reactive to the initial EIA test. Of these, 3664 (56%) were nonreactive with RPR testing. Additional testing of 2512 of these 3664 RPR-nonreactive samples with a different treponemal-specific test found that 2079 (83%) were also reactive to the second treponemal test.

There are several possible explanations for a positive EIA and a negative RPR, including (1) successful treatment of a previous syphilis infection resulting in seroreversion of the RPR; (2) spontaneous seroreversion of RPR titers in an untreated individual with long-standing syphilis; (3) very early syphilis infection (some studies have shown that treponemal-specific tests may become positive before the RPR); or (4) a false-positive EIA test. Clinical information was not available in the MMWR study. Thus, it is impossible to determine the cause of the serodiscordance. When interpreting discordant test results, a clinical history is of paramount importance; for patients who provide a history of previously treated syphilis, no further testing is warranted. In contrast, for those who do not recall a prior history of syphilis, additional evaluation is warranted. One approach is to obtain a different treponemal-specific test. If that test is positive (thereby confirming the EIA result), then patients who have no previous history of treated syphilis should be staged and treated appropriately (if asymptomatic, most of those patients would be treated for late latent syphilis or syphilis of unknown duration with 3 doses of 2.4 million units of long-acting intramuscular benzathine penicillin G over 2 weeks). The CDC is preparing a statement on the appropriate approach for managing serodiscordant syphilis test results.

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