Perspective

What’s New in Sexually Transmitted Infections in the HIV Care Setting: Focus on Syphilis and Gonorrhea

Sexually transmitted infections are a resurgent problem in HIV disease. The number of new cases of syphilis among men who have sex with men has continued to increase, requiring renewed vigilance in screening, diagnosis, and treatment. Drug-resistant gonorrhea has prompted changes in treatment regimens and warrants continued monitoring. This article summarizes an IAS–USA continuing education webinar presented by Jeanne M. Marrazzo, MD, MPH, in January 2014.

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Sexually transmitted infection (STI) acquisition and risk-taking behavior are ongoing among some HIV-infected patients in primary care. Data reported in 2012 from a prospective cohort study of 557 HIV-infected adults in primary care in 4 US cities showed that 13% had STIs at time of enrollment and 7% had an incident STI within 6 months of enrollment.1 Excluding trichomoniasis, 94% of the incident STIs were among men who have sex with men (MSM), with 20% of MSM diagnosed with an STI within 6 months. The most common infections in men were rectal chlamydial infection and oropharyngeal gonorrhea. Risk factors for infection included polysubstance use and having more than 4 sexual partners within 6 months.

New Syphilis Epidemic

Data from the Centers for Disease Control and Prevention (CDC) for the period from 2007 to 2013 showed that although the annual number of new cases of primary and secondary syphilis remained steady or declined among women and among men who have sex exclusively with women, it increased by 7% among MSM from 2012 to 2013.2

The presentation of syphilis can be particularly diverse in the context of HIV infection. Findings have included lues maligna, a very invasive skin disorder, and increased frequency of clinically significant symptomatic neuroinvasive disease, especially auditory or ocular neuropathy.

The latent stage of syphilis is characterized by positive treponemal serology in the absence of clinical manifestations, with early (seroconversion within 1 year of infection) and late (seroconversion after 1 year) latency periods characterized by evidence of seroconversion. Approximately two-thirds of individuals with untreated syphilis remain in the latent stage for life.

Screening

Traditionally, syphilis screening involved nontreponemal tests, such as the rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) assays. These tests provide quantitative results that can be followed over time to assess treatment response. Findings would then be confirmed by qualitative treponemal testing with, for example, a Treponema pallidum particle agglutination or a fluorescent treponemal antibody assay. This traditional screening approach is being replaced by reverse screening, in which qualitative treponemal testing is performed first with enzyme, chemiluminescence, or microbead immunoassays—automated tests that are easier to perform—and then followed by quantitative RPR or VDRL testing. This reverse sequence screening algorithm for syphilis is shown in Figure 2.3

Neurosyphilis

Neurosyphilis can occur at any stage of syphilis. Central nervous system (CNS) invasion occurs early in syphilis infection in approximately 30% to 40% of cases and is asymptomatic in the majority of patients. Early symptomatic

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forms of neurosyphilis, which may occur within months or years of infection, include acute syphilitic meningitis with neuropathy of auditory, optic, and facial nerves (cranial nerves VI, VII, and VIII); meningovascular stroke (stuttering stroke); and altered mental status. CNS gummas have been observed earlier in the brains of HIV-infected patients with syphilis than in the brains of HIV-uninfected patients with syphilis. Later symptomatic presentations of neurosyphilis (eg, occurring after 2 years) include general paresis and tabes dorsalis. Ocular syphilis can manifest as posterior chamber uveitis, retinitis, or retinal detachment.

There are data indicating that CNS invasion is more likely to occur among HIV-infected patients with CD4+ cell counts of 350/µL or lower or RPR titers of 1:32 or higher. However, there are no data supporting better outcomes of neurosyphilis treatment among such patients in the absence of neurologic symptoms. Thus, lumbar puncture for cerebrospinal fluid (CSF) collection is not recommended in the absence of neurologic symptoms. Patients should be carefully evaluated for neurologic, ophthalmic, and otologic symptoms, and lumbar punctures should be performed for those who are symptomatic.4,6

A CSF VDRL test, the only diagnostic test approved for use on CSF specimens, is highly specific but relatively insensitive in diagnosis. Among HIV-infected patients with neurologic symptoms and negative CSF VDRL test results, treatment can be considered for pleocytosis of greater than 20 white blood cells/µL (a higher threshold than for HIV-uninfected patients, as HIV infection itself is associated with CSF inflammation).7,8 The CSF fluorescent treponemal antibody test is not highly sensitive but is specific; a negative test result may help to rule out neurosyphilis, although it should not rule out infection if clinical suspicion is high.

**Treatment**

Syphilis treatment has remained largely unchanged for decades. For primary, secondary, and early latent syphilis, recommended treatment is a single intramuscular (IM) dose of long-acting benzathine benzylpenicillin 2.4 million U. Other penicillin formulations or azithromycin should not be used. Doxycycline 100 mg taken orally twice daily for 14 days may be used but is inferior to benzathine benzylpenicillin.9 Intravenous or IM ceftriaxone 1 g taken daily for 8 days to 10 days may be used as an alternative treatment to doxycycline but is a challenging regimen to administer, given that it involves the daily injection of a drug that requires refrigeration at a clinic and that the IM injection can be painful.7,10 For late latent syphilis, standard treatment is 3 weekly doses of IM benzathine benzylpenicillin 2.4 million U; a 28-day, oral doxycycline regimen is an inferior alternative. For neurosyphilis, standard treatments are aqueous penicillin G 18 million to 24 million U daily for 10 days to 14 days, or procaine penicillin G 2.4 million U plus oral probenicid 500 mg daily for 10 days to 14 days. Daily intravenous ceftriaxone 2 g for 10 days to 14 days may be used as an alternative.

**Gonorrhea**

There has been an increasing number of reports of clinical *Neisseria gonorrhoeae* isolates with resistance to cephalosporins, including reports of patients with gonorrhea resistant to extended-spectrum parenteral agents.

The Gonococcal Isolate Surveillance Project (GISP), a collaborative project of the CDC, monitors trends in gonococcal antibiotic susceptibility among men attending STI clinics. Urethral antibiotic susceptibility among men attending STI clinics.

Figure 1. Varied presentations of primary and secondary syphilis infection. Photographs courtesy of University of Washington Sexually Transmitted Disease Training Center.
used in this setting irrespective of whether a patient has chlamydial infection, for which it is also indicated. If there is absolutely no way to administer IM ceftriaxone, a single dose of oral cefixime 400 mg may be used with azithromycin or doxycycline. It is also recommended that IM ceftriaxone 250 mg be used for pharyngeal infections, which are notoriously difficult to eradicate. Vigilance should be maintained for gonococcal persistence.

In cases of treatment failure, an infectious diseases specialist should be consulted, culture and susceptibility testing performed, treatment with IM ceftriaxone (250 mg) plus azithromycin (2 g) attempted, partner treatment ensured, testing for cure completed 1 week after treatment, and the case should be reported to the CDC via state or local public health departments. Unfortunately, there have been at least 2 case reports of treatment failure with gonococcal isolates with high-level resistance to azithromycin, a situation that must be closely monitored.13

It is now recommended that a test of cure, by culture or nucleic acid amplification test (NAAT), be performed in patients not receiving a ceftriaxone regimen.14 Although testing is recommended at 7 days after treatment, there are few data on the likelihood of negative NAAT results at 7 days with adequately treated infection. It is therefore reasonable to wait until 10 days after treatment to complete an NAAT.

Recent reports on new treatments have included good results with the aminoglycoside gentamicin or the quinolone gemifloxacin in combination with azithromycin 2 g.15 New agents under investigation include solithromycin, dalbavancin, MUT056399 (an inhibitor of fatty acid biosynthesis enzyme), pleuromutilins, bicyclolides, ketolides, nonquinolone topoisomerase inhibitors, and host defense peptides with direct or indirect antibacterial activity. New targets under investigation include gonococcal lipid A and efflux pumps.

The United Kingdom now recommends ceftriaxone 500 mg (rather than the 250 mg dose used in the United States) plus azithromycin instead of cefixime. This change appears to have been accompanied by a reduction in the percentage of isolates with cefixime resistance, from 17.1% in 2010 to 10.8% in 2011.16 Whether this indicates a causal relationship remains to be determined.

Screening

Annual screening for rectal gonorrhea is important for patients who report engaging in receptive anal sex (regardless of whether they report condom use), particularly because rectal gonorrhea is associated with increased HIV shedding. Similarly, annual screening for pharyngeal infection should be performed for patients who report

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**Figure 2.** Reverse sequence screening algorithm for syphilis infection. CIA indicates chemiluminescence immunoassay; EIA, enzyme immunoassay. Adapted from Centers for Disease Control and Prevention.3

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conducted by the CDC. As shown in Figure 3, data from GISP indicate that the percentage of isolates with elevated minimum inhibitory concentrations (MICs) of cefixime has increased steadily in the western United States and among MSM.11 In 2010 and 2011, approximately 1.4% of isolates had resistance to cefixime, with the percentage decreasing to approximately 1% in 2012.

There has also been an increase in the percentage of isolates with elevated MICs of ceftriaxone, although the percentage of resistant isolates is not as high as seen with cefixime. Steady increases to 0.3% in 2010 and 0.4% in 2011 were followed by a decline to below 0.3% in 2012. It remains to be seen whether the recent declines in prevalence of isolates resistant to these agents indicate beneficial trends. GISP data indicate that the problem with cephalosporin resistance is occurring largely among MSM. Data from 2005 to 2010 indicated isolates with elevated MICs of cefixime and ceftriaxone in 1.7% and 0.4%, respectively, of 8117 MSM and in 0.2% and 0.1%, respectively, of 26,483 men who have sex exclusively with women.12

**Figure 3.** Percentage of gonococcal isolates with elevated minimal inhibitory concentrations (MICs) of cefixime (≥0.25 µg/mL), by US region or by sexual risk behavior, from 2005 to 2011. Testing was not performed in 2007 or 2008; therefore, data for this time period are unavailable. Adapted from Bolan et al.11

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**Treatment**

For uncomplicated gonorrheal infections of the cervix, urethra, or rectum, recommended treatment is a single IM dose of ceftriaxone 250 mg plus either azithromycin 1 g or doxycycline 100 mg twice daily for 7 days. Azithromycin is the preferred choice and should be

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**Table 1.** Syphilis screening algorithm. CIA indicates chemiluminescence immunoassay; EIA, enzyme immunoassay. Adapted from Centers for Disease Control and Prevention.

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engaging in receptive oral sex, as pharyngeal infection appears to offer the opportunity for gonorrhea to acquire mutations from other Neisseria species, which can result in reduced drug susceptibility.

Other STIs

Hepatitis C Virus

There has been an increase in incidence of hepatitis C virus (HCV) infection among MSM, beginning in approximately 2004 and accelerating in recent years.17 Risk factors include unprotected receptive anal intercourse and rough or poorly lubricated, unprotected anal penetration. Current guidelines recommend HCV testing for all HIV-infected patients, injection drug users, and anyone born between 1945 and 1965. Acute infection may be HCV antibody negative. HCV RNA level should be tested in patients with new, unexplained transaminase elevation.

Anal Dysplasia and Cancer

Primary care guidelines from the HIV Medicine Association of the Infectious Diseases Society of America recommend anal Papanicolaou (Pap) testing in patients with a history of receptive anal intercourse, abnormal cervical Pap results, or genital warts.18 Patients with abnormal anal Pap results should be evaluated with high-resolution anoscopy. Human papillomavirus (HPV) DNA screening is not recommended, and its role remains undefined. HPV vaccination is safe and immunogenic for HIV-infected patients and has been shown to prevent anal cancer and anal intraepithelial neoplasia. The introduction of HPV vaccination has resulted in declines in the prevalence of vaccine and nonvaccine high-risk HPV types among young women in the United States and a decline in the prevalence of genital warts in Australia among younger age groups.19,20

Conclusions

HIV-infected patients should be screened for syphilis, gonorrhea, and chlamydia infections at entry to care and periodically thereafter, depending on risk. Rectal testing for gonorrhea and chlamydia infections should be performed for patients who report engaging in receptive anal sex, and oral testing for gonorrhea should be performed in those who report engaging in receptive oral sex. Rescreening for chlamydial and gonococcal infections should be performed 5 months to 6 months after an initial positive test result.

Practitioners should be aware of enzyme immunoassays for syphilis detection and how to use them and should be able to recognize neuroinvasive disease. Vigilance should be maintained when gonorrhea is antibiotic resistant. Patients should receive HPV vaccination but should also continue to undergo Pap screening.


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References


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