Sexually Transmitted Diseases: Diagnosis and Work-Up (GC, Chlamydia, Herpes, HPV)

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Abstract

There is an array of tests available to diagnose each of the above sexually transmitted diseases. Each test has its own sensitivity, specificity, and specific clinical situation for which it is ideally situated. Nucleic acid amplification tests (NAATs) tend to have the highest sensitivity and specificity when testing for gonorrhea and chlamydia. However, depending on the clinical scenario and site to be tested, there may be other tests which are better suited. Testing for HSV lesions has variable sensitivity and specificity based on the time interval between testing and outbreak and amount of viral shedding. To negate this variability, indirect testing which exams the patient's blood for antibodies to HSV has been created. This test can detect antibodies against HSV, even after lesions have resolved. The human papillomavirus is extremely prevalent worldwide. Cytology and HPV co-testing still remain the gold standard for diagnosing and triaging HPV. A thorough knowledge of the common presentation, available testing, and current treatments is essential for all healthcare providers. Early detection, diagnosis, and treatment will prevent continued spread to other parties and decrease morbidity in patients.

The purpose of this chapter is to present the current standards for diagnosis and treatment of sexually transmitted diseases. In this text, presentation, diagnosis, and treatment of the sexually transmitted diseases, gonorrhea, chlamydia, herpes simplex virus, and human papillomavirus, are discussed. In order to obtain the most current and accurate data, a comprehensive literature review was performed for each of the abovementioned sexually transmitted diseases in regard to presentation, available screening and diagnostic testing, and treatment. The CDC database was cross-referenced to confirm concordance in the treatment of the abovementioned sexually transmitted diseases.

Keywords

Gonorrhea • Chlamydia • Human papillomavirus • Herpes simplex virus • Screening • Sexually transmitted infections

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1 Introduction

According to the Centers for Disease Control and Prevention in 2008, there was an estimated 20 million new cases of sexually transmitted diseases diagnosed, with a prevalence of 110 million. The estimated healthcare cost for treatment and diagnosis of these diseases was approximately $16 billion. The breakup of disease burden is roughly equal for men and women. The prevalence of disease is highest in those 30 years of age and younger. Many of the most prevalent sexually transmitted diseases such as gonorrhea and chlamydia have effective treatments available that prevent major complications. If untreated, the infection may progress and cause tubal damage, require extended antibiotic treatment, or even become life threatening. For this reason, it is imperative that the clinician be aware of the appropriate screening and diagnostic tests available to identify sexually transmitted diseases. Often patients are asymptomatic. For this reason, routine screening of individuals at risks for sexually transmitted disease is encouraged. The indications for screening are listed below (CDC 2013) (Table 1).

2 *Chlamydia trachomatis*

2.1 Epidemiology

Chlamydia is the second most prevalent STD in the United States with the highest prevalence in less than 25 years of age group. Given the asymptomatic nature of the disease for a majority of women and the high prevalence, yearly testing is advised for women less than 25 years old. Screening should be done in all women less than 25 years old and in women over 25 years of age with any of the following risk factors: new or multiple sexual partners, inconsistent condom use, sex worker, current STD, or history of STDs (Williams 2012). While infections are often asymptomatic, symptoms can include mucopurulent discharge, endocervical secretions, and hyperemia of the infected tissue/edema. If the infection affects the urethra, urethritis is common and often associated with prominent dysuria, frequency, and/or urgency (Williams 2012). Untreated chlamydial infections can lead to serious complications such as pelvic inflammatory disease (PID), subsequent infertility, and increased risk of ectopic pregnancy. The implementation of routine screening of women 25 years old and less has led to a decrease in serious complications such as PID. Currently, there are no suggestions for the routine screening of asymptomatic men (CDC 2015a).

2.2 Screening and Testing

There are many tests available to screen and diagnose chlamydia. The most often used tests include the use of nucleic acid amplification tests (NAATs), direct fluorescent antibody (DFA), enzyme immunoassay (EIA), and tissue culture (Carder et al. 2006). Testing for chlamydia relies

Table 1 Indications for sexually transmitted disease screening

Sexually transmitted disease	Indications for screening	Risk factors	Treatment
Chlamydia trachomatis	Age 25+ with risk factors	Prior STI; new partner, multiple partner, sex work, intercourse without condoms	Azithromycin 1 g po × 1
	Under age 25		
	Women with cervicitis		
	All pregnant women in first trimester, again in third trimester if high risk		
Neisseria gonorrhoeae	Age 25+ with risk factors, under age 25	Prior STI; new partner, multiple partner, sex work, intercourse without condoms	Ceftriaxone 250 mg IM × 1 + azithromycin 1 g po × 1[a]
Herpes simplex virus	Not indicated [only if a suspected lesion is present or if partner has HSV]	Number of sexual partners	Acyclovir 400 mg po TID × 7–10 days (and others)
Human papillomavirus	Reflex testing for women age 21–30 every 3 years or routine screening age 30–65 every 5 years	Number of partners	None
		Age of first intercourse	

[a]Adapted from Williams Gynecology 2nd edition; Chapter 1 Well Woman Care; Patient Education Fact Sheet, New Guidelines for Cervical Cancer Screening, Sept 2013

heavily on the use of NAATs given their high sensitivity and fast turnaround time.

NAATs have the ability to produce a positive signal from a single copy of RNA or DNA. This has led to their high sensitivity, especially when compared to other forms of testing; however, no test can give 100% sensitivity (Carder et al. 2006). Given the high sensitivity of NAATs, there is only another NAAT sensitive enough to confirm a positive result. If test results are equivocal, then the original sample should be retested rather than collecting a new specimen. NAATs can be used for a variety of locations including first-catch urine specimens, cervical, urethral, and rectal:

- Tissue culture is the preferred test for rectal specimens but when unavailable NAATs are the test of choice (Carder et al. 2006).

DFAs use fluorescent-labeled antibodies that bind to *C. trachomatis*. Typically a swab is used to sample the sites suspicious for *C. trachomatis*. Following sampling, the swab contents are placed on a slide and allowed to dry. In the lab, antibodies that bind to *C. trachomatis* are then placed over the sample and the slide is viewed under a fluorescence microscope. Visualization of florescence yields a positive result, while absence of florescence yields a negative result. Sensitivity and specificity are dependent on the laboratory:

- Given that DFAs must be viewed individually under a microscope, DFAs are best suited for detecting *C. trachomatis* in small number (Carder et al. 2006).
- DFAs can be used to detect *C. trachomatis* from cervical, urethral, pharyngeal, and rectal specimens. DFAs can be used with first-catch urine but it is not ideal.

EIAs use monoclonal and polyclonal antibodies labeled with an enzyme to detect the specific lipopolysaccharide within *C. trachomatis*. If present, the enzyme converts a colorless substrate into a colored product that is then detected by using a spectrophotometer. The antibodies in this EIAs can cross-react with other microorganisms that contain LPS such as other *Chlamydia* species. When an EIA yields a positive result, confirmatory testing should be done by either DFA or using a blocking antibody that has been developed to verify positive EIA rest results. Sensitivity for EIA is less than that for DFA (Carder et al. 2006). EIAs can be used to collect specimens

from cervical and urethral specimens and in first-catch urine from symptomatic men.

Tissue culture for *C. trachomatis* is now a test with limited use in clinical practice. This was previously the traditional gold standard for testing. However, with the advent of new tests such as the NAATs, DFAs, and EIAs, there are very few laboratories that will still perform tissue culture for *C. trachomatis* given that cell cultures are very labor intensive and expensive and take several days for a positive result:

- There are several instances when culture is the preferred testing method. In cases of sexual assault or abuse, tissue culture is the preferred method because it allows clinicians and law enforcement agencies to definitively identify the organism causing the infection.
- In addition, tissue culture is the test of choice in diagnosing *C. trachomatis* from rectal specimens.
- Tissue culture is suitable for specimens collected from the cervix, urethra, and pharynx, but given the aforementioned limitations, it is not routinely used (Papp et al. 2014).

Test of cure (TOC) is not routinely done if the patient has been treated, if there is confirmation that the patient complied with treatment, and if there is no risk of reinfection. If the clinician is in doubt, a TOC should be performed. Given the morbidity associated with *C. trachomatis* to the developing fetus, TOC should be routinely done in all pregnant patients. TOCs are typically completed 3–5 weeks posttreatment. TOC performed sooner can cause false-positive results secondary to residual RNA or DNA from the organism:

- CDC recommends that clinicians contact local or state health department for guidance to arrange for antimicrobial susceptibility from patients failing treatment with CDC-recommended regimens. Ideally, TOC and evaluation of antibiotic efficacy can only be performed via tissue culture. NAATs and DFAs are not FDA approved for this purpose (Papp et al. 2014).

2.3 Sites for Testing

Given the numerous mucosal surfaces that *C. trachomatis* can infect and the numerous tests available to screen and diagnose *C. trachomatis* infections, it is imperative that the clinician be familiar with which tests are appropriate to use with each site of testing (summarized in Table 2):

- First-catch urine is one of the simplest samples to collect. Ideally the urine specimen should be collected from the first 30 cc of urine. NAATs are the preferred method of testing for first-catch urine. EIAs are highly sensitive in the symptomatic male but not in asymptomatic males or females in general. If NAATs are unavailable, DFA can be used but are not ideal. Culture of first-catch urine is typically not appropriate.
- Cervical and urethral specimen sites are suitable for all the abovementioned testing modalities.
- Vaginal swabs can be collected by either the physician or the patient. Studies have shown high sensitivity when vaginal swabs are tested with NAATs with sensitivity >95%. The sensitivity in physician- vs. patient-collected vaginal specimens was not statistically significant. Several studies demonstrated a higher sensitivity in vaginal specimen than endocervical specimen (95% vs. 90%). In addition, patient-collected vaginal swabs are better tolerated by the patient and provide less discomfort,

Table 2 Sample collection site for *C. trachomatis*

Testing site	Approved methods
Urine (first 30 cc's)	NAATs
	EIAs in male urine
Vaginal	NAATs
Cervical	NAATs, DFAs, EIAs, culture
Oropharynx	Culture
	DFAs-acceptable
Rectal obtained via proctoscopy	Culture
	DFAs-acceptable
Urethral	NAATs, DFAs, EIAs, culture

especially in the pediatric and adolescent age groups (Schachter et al. 2005).

- Given the recent changes of sexual practices, the oropharynx and rectum are being found to be sites of infection with *C. trachomatis* more commonly. The oropharynx and rectum are best tested with culture or DFA (Carder et al. 2006).

2.4 Treatment

There are many treatment regimens available for chlamydia. The main concerns for treating chlamydia is early intervention to reduce the risk of PID, patient compliance, abstinence during the treatment window, and treating of infected partners. In the pregnant population, early treatment has been shown to decrease the risk of transmission to the neonate/fetus:

- In patients whom compliance to treatment is of concern, azithromycin 1 g orally onetime dosing has been proven to treat chlamydia and is considered a first-line treatment. In patients who are unable to tolerate azithromycin secondary to allergies or side effects, doxycycline 100 mg orally twice daily for 1 week has been proven to be equally as effective (98% and 97% response rates, respectively) (CDC 2015a).
- A 200 mg po extended release daily doxycycline regimen has been tested and found to be equally as effective as the 100 mg twice daily regimen, but is considerably more expensive. Doxycycline is contraindicated in the second and third trimester of pregnancy; for this reason, treatment with azithromycin is the preferred method of treatment.
  - Given the risk to the neonate in the instance when chlamydia is not completely treated, a test of cure is recommended 3–4 weeks after completing treatment (CDC 2015a).
- Other treatment regimens are available such as erythromycin 500 mg orally four times daily for 7 days or levofloxacin/ofloxacin for a 7-day course. Treatment with erythromycin is not as effective as azithromycin and has been associated with more gastrointestinal side effects.
- Levofloxacin and ofloxacin are also effective in the treatment of chlamydia but are relatively more expensive and have not shown any superiority to treatment with azithromycin or doxycycline. For this reason, azithromycin and doxycycline are considered first-line treatments (CDC 2015a) (summarized in Table 3).

One aspect of treatment of chlamydia is patient education. It is imperative to educate the patient about risk of reinfection if their partner is not treated, informing all sexual contacts so that they may be treated as well, and for patients to abstain from sexual intercourse for 7 days after receiving onetime treatment or to abstain from sexual intercourse for the entire treatment duration for the 7-day antibiotic course and to wait for symptoms to resolve. Failure to comply with the above greatly increases the risk of reinfection (CDC 2015a).

2.5 Expedited Partner Therapy in Management of Chlamydia and Gonorrhea Infection

The American College of Obstetricians and Gynecologists [ACOG] supports the use of expedited partner therapy when a patient's partner is unwilling or unable to seek medical care. ACOG

Table 3 Treatment of chlamydia

Treatment	
Azithromycin 1 g po ×1	First-line treatment
Doxycycline 100 mg po BID ×7days[a]	First-line treatment
Erythromycin 500 mg po QID ×7 days	Second-line treatment
Erythromycin ethylsuccinate 800 mg po QID ×7 days	Second-line treatment
Levofloxacin 500 mg po ×7 days	Second-line treatment
Ofloxacin 300 mg po BID ×7 days	Second-line treatment

[a]Delayed release 200 mg po doxycycline regimen ×7 days has been studied and is equally efficacious, but more expensive

recommended that therapy should be accompanied with treatment instructions along with a recommendation that they seek medical attention as soon as possible. (ACOG Committee Opinion 2015)

3 *Neisseria gonorrhoeae*

3.1 Epidemiology

Neisseria gonorrhoeae is a gram-negative diplococcus bacterium which is transmitted through sexual activity. According to recent CDC publications, it is estimated that there are approximately 700,000 new cases of gonorrhea every year in the United States, making it the second most common bacterial sexually transmitted disease (Bleich et al. 2012). Gonorrhea is often asymptomatic or only presents with odorless white/yellow vaginal discharge. Other symptoms of gonorrhea include abnormal vaginal discharge, abnormal vaginal bleeding after intercourse, intermenstrual spotting, genital itching, and pain. Gonorrhea can cause ascending infections in the female genital urinary tract and systemic illness. Systemic gonorrhea, also known as disseminated gonococcal infection, has a prevalence reported as high as 0.5–3% after untreated mucosal infection (Bleich et al. 2012). Initial symptoms can present with fevers, arthralgia, rash, migratory polyarthritis, septic arthritis, and tenosynovitis. Severe cases of disseminated gonococcal infection can result in endocarditis and meningitis (Bleich et al. 2012).

Compared to women, a larger percentage of men are symptomatic from *N. gonorrhoeae* infection that often leads to earlier treatment before sequel, but typically not before transmission has occurred. Women typically are asymptomatic at initial time of infection and may later present with pelvic inflammatory disease (PID) associated with *N. gonorrhoeae* infections. PID can lead to hospitalization, scarring of the fallopian tubes, and future increased risk of ectopic pregnancy or infertility. For these reasons, accurate and rapid diagnosis of gonorrhea is critical in the healthcare setting.

Given the asymptomatic nature of the disease in a majority of women and high prevalence, yearly testing is advised in women less than 25 years of age. Screening should be undertaken in all women less than 25 years old or if any of the following risk factors: new or multiple sexual partners, inconsistent condom use, sex worker, current STD or history of STDs, or previous infection with *N. gonorrhoeae* (Williams 2012).

3.2 Screening and Diagnostic Testing

There are various forms of testing available for screening and diagnosing gonorrhea including microscopy, culture, nucleic acid amplification tests, and nucleic acid hybridization test. These tests are commonly used in the healthcare setting and each has their preferred site of testing and particular advantages:

- Direct microscopy has both high sensitivity and specificity in the symptomatic patient population (95%, 99%). The identification of gram-negative intracellular diplococci and polymorphonuclear leukocytes on microscopy is considered diagnostic for gonorrhea. The sensitivity of direct microscopy is greatly decreased in the asymptomatic patient population. When used in patients who are asymptomatic as a screening tool, the sensitivity is only 50–75%. However, the specificity of direct microscopy remains about 99% in both the symptomatic and asymptomatic patient populations (CDC 2015a).
- Culture has long been used for testing of gonorrhea. Culture has many advantages, one being that it can use specimens from all sites as long as there are viable organisms. Sensitivity is comparable to other forms of screening and diagnosing with a sensitivity of 85–95% for urethral and endocervical specimens. In addition, cultured specimens can be sent for susceptibility testing. However, isolating gonorrhea can be cumbersome. Given the polymicrobial nature of many of the sites cultured

for gonorrhea, selective enriched medium with supplementation must be used. Antimicrobial agents are commonly used with the culture media to select only for gonorrhea (Bignell et al. 2006).

- One of the drawbacks of culture is the fact that a viable specimen must be collected in order to have a positive result. This is not the case for tests that rely on nucleic acid sequences. Nucleic acid hybridization or amplification tests can use nonviable specimens from samples such as urine or self-taken swabs. The sensitivity has been reported to be as high as 95% for endocervical and urethral samples. One drawback to the use of nucleic acid tests is that they do not necessarily have a viable organism to which susceptibility testing can be performed. However, as discussed below, treatment for *N. gonorrhoeae* infection typically consists of one dose of 250 mg of intramuscular ceftriaxone with 1 g of azithromycin orally. Specificity remains high in the nucleic acid tests with reports as high as 99%. Given the high sensitivity of NAATs, they are currently considered the gold standard for detection of *N. gonorrhoeae* (Bignell et al. 2006).

3.3 Sites for Testing

Many sites are at risk for infection with gonorrhea. The most common are mucosal sites, but systemic and ophthalmic sites are susceptible to infection as well. Any mucosal site associated with the common symptoms of gonorrhea should undergo testing. The appropriate test to detect gonorrhea will depend on the site the specimen is to be obtained from, the normal flora of these sites, and the indication for testing (Table 4). For example, NAATs are a highly used method of testing for many mucosal sites, such as the endocervix. However, in cases where abuse or sexual assault is of concern, tissue culture is the preferred method (CDC 2014). One of the easiest samples to obtain is patient-collected vaginal samples. These samples are ideal for patients who have symptoms but are adverse or hesitant to undergo a speculum examination. Many clinicians find this an acceptable form of testing for the pediatric and adolescent population (Schachter et al. 2005). NAATs have a high sensitivity and are an acceptable form of testing:

Table 4 Testing sites for gonorrhea

Testing site	Appropriate test
Endocervix	NAATs, microscopy, culture
Urethra	Microscopy, culture, NAATs[a]
Vagina	NAATs
Urine	NAATs
Rectum	Culture
Oropharynx	Culture

[a]NAATs are less sensitive for urethral specimens in asymptomatic male

- Since there is still the possibility of cross-reactivity and false positives with other vaginal flora, in situations where rape or abuse is suspected, culture remains the preferred method of testing.
- Urine is another commonly used noninvasive specimen which can be used for screening and diagnostic testing. The sample should typically be obtained from the first 30 ml of voided urine. Urine samples are best tested using NAATs.
- The endocervical sample from women can be used to test for all methods. Drawback to the endocervical collection are necessity of speculum exam which sometimes deters patients and use of vaginal lubricant. Vaginal lubricant has been shown to be toxic to gonorrhea (Bignell et al. 2006) and can lead to a nonviable specimen. Urethral samples are another mucosal site which can be appropriately tested using the abovementioned tests.
- The rectum and oropharyngeal sites are unique from other mucosal sites for testing. These mucosal sites are populated by normal flora and consistent of many gram-negative rods and cocci (Todar 2012). Given the high prevalence of other bacteria which populate these sites, NAATs have a high rate of false positives. The nucleic acid composition of other bacteria can cross-react and lead to false positives. The same can be said for microscopy and gram stain. Given that these two mucosal sites

are heavily populated with other flora, microscopy with gram stain is difficult secondary to the presence of other bacteria. For this reason, culture is the best way to identify *N. gonorrhoeae* infection in the rectum or oropharynx (USPTF 2014).

3.4 Treatment

N. gonorrhoeae is a highly resistant bacterium to the majority of antibiotics available. *N. gonorrhoeae* easily mutates and can easily acquire resistance to many classes of antibiotics. Given this reason, there is a theoretical benefit to treating gonorrhea with two classes of antibiotics to improve the efficacy of treatment and decrease the probability of gonorrhea acquiring resistance to current treatment. In addition, persons infected with gonorrhea are at higher risk for coinfection with chlamydia:

- For this reason, treatment with a cephalosporin and with azithromycin is the standard of care. Gonorrhea is typically treated with ceftriaxone 250 mg IM ×1 and azithromycin 1 g po ×1. This onetime dosing is favorable because it ensures patient compliance when given in the office setting. In the setting when ceftriaxone is unavailable, substitution with the cephalosporin cefixime is acceptable. However, cefixime does not achieve the same bactericidal blood levels as compared to ceftriaxone and can have decreased efficacy, especially for treatment of pharyngeal infection (CDC 2010).
- An alternative treatment with doxycycline 100 mg po BID for 7 days is available with those who are unable to tolerate azithromycin secondary to allergies or side effects (summarized in Table 5).

Test of cure is not routinely done after treatment is given except in patients who have persistent symptoms or represent with symptoms shorty after completion of treatment (Williams 2012). If a patient fails treatment with the recommended cephalosporin, culture should be performed to evaluate for antibiotic (CDC 2015a).

Table 5 Treatment of gonorrhea

Antibiotic regimen	
Ceftriaxone 250 mg IM × 1 + Azithromycin 1 g po ×1[a]	Preferred regimen
Cefixime 400 mg po × 1 + azithromycin 1 g po ×1[a]	If ceftriaxone unavailable
	TOC should be performed in 1 week
Azithromycin 2 g po × 1	If patient has severe allergy to cephalosporin

2010 CDC STD treatment guidelines
[a]Doxycycline 100 mg po BID ×7 days is an acceptable alternative to azithromycin in patients who are unable to tolerate azithromycin

4 Herpes Simplex Virus Types 1 and 2

4.1 Background

The herpes simplex virus is a common viral infection found in the United States. There are two subtypes: HSV-1 and HSV-2. HSV-1 is often associated with orolabial transmission and is not considered a sexually transmitted disease. A large proportion of the United States population is infected with HSV-1. HSV-1 can be found in a proportion of the pediatric population and it can be spread by kissing. A large majority of people who are carriers of HSV-1 are asymptomatic and lesions only present at times of stress or if immunocompromised. Lesions typically consist of superficial ulcerations along the oral cavity, sometimes referred to as cold sores.

HSV-2 however is commonly the cause of genital herpes and transmitted through anogenital contact. HSV-2 is considered a sexually transmitted disease. Most HSV infections occur between ages 15 and 35. HSV-1 does not provide protection against HSV-2 but there is some protection against HSV-1 in individuals infected with HSV-2 (Eckert and Lentz 2012).

Subclinical herpes infections are common, but primary infections typically present with both systemic and local symptoms. Systemic symptoms can include fever, fatigue, and malaise. These symptoms are reported in 60–80% of

primary herpes infections (Eckert and Lentz 2012). Local symptoms of the infected tissue include paresthesia of the surrounding skin, severe pain, inguinal lymphadenopathy, appearance of multiple vesicles, superficial ulcers, and pain. Severe symptoms typically last 10–14 days; however, it may take up to 6 weeks for lesions to heal. Since the ulceration is typically superficial, the lesions generally heal without evidence of scarring. During the primary infection, viral cultures yield a positive result 80% of the time (Eckert and Lentz 2012).

Recurrence is common in HSV infections and frequency is related to serotype and severity of the initial infection. Those with HSV-1 have a 50–60% risk of recurrence within the first 12 months after the initial infection, whereas those with HSV-2 typically have an 80% risk of recurrence within the first 12 months. If the initial presentation was severe, recurrence is typically twice as often. Culturing of recurrent herpes lesion only yields a positive result in 40% of cases (Eckert and Lentz 2012).

4.2 Testing for HSV-1 and HSV-2

There are several methods available for testing for infections with herpes simplex virus. Some rely on culturing of the virus, often referred to as direct testing. Others rely on identification of type-specific antibodies in the patient's blood. This second form of testing is commonly referred to as type specific or indirect testing (Singh et al. 2005).

1. Direct testing includes viral culture, Tzanck smears, DFAs, PCR, and rarely electron microscopy. Direct testing is an appropriate method of testing for patients who present with acute ulcerative lesions and are seeking diagnosis and treatment of their active lesions. One of the challenges of direct testing is the variability of sensitivity among these tests. Sensitivity is the highest for direct testing at the time of onset of the lesions. As the acute lesions begin to heal, the presence and ability to successfully collect viable virus decreases rapidly. Since direct testing relies on collecting viral specimens from the acute lesion, the sensitivity for direct testing falls drastically as the lesions begin to heal (Singh et al. 2005). A negative test does not necessarily mean that the patient is not infected with herpes, especially in a nonacute or asymptomatic patient. Since asymptomatic patients typically have intermittent viral shedding, direct testing is not the test of choice for asymptomatic patients given the very low sensitivity in this clinical scenario.
   - Viral culture has long been the gold standard for the diagnosis of HSV lesions. Specificity is recorded at 100%. Sensitivity however is variable. With time, the HSV lesions will begin to heal, as the lesions heal, the sensitivity of viral culture sharply falls. Once crusting is demonstrated around the HSV lesion ulcers, the sensitivity markedly lower than for acute lesions. Sensitivity has been reported around 75% for primary lesions and 50% for recurrent lesions (Singh et al. 2005).
   - Tzanck smears have been used to detect HSV infections. They rely on the identification of cytopathic changes in genital epithelial cells. Infected cells typically will be enlarged with multinucleated cells with clear inclusions. Typically, the Tzanck smear is prepared with the Wright-Giemsa stain and examined under the microscope. The Tzanck smear cannot differentiate between HSV-1 and HSV-2, and the test can be positive with the presence of the varicella zoster virus. The Tzanck smear does not replace other diagnostic testing, but rather serves as a way to aid in immediate diagnosis when other testing modalities are unavailable (Singh et al. 2005).
   - Herpes PCR is considered the test of choice for diagnosing HSV infections of the central nervous system such as meningitis or encephalitis. In the setting of HSV central nervous system infections, PCR has greater sensitivity and detection than viral culture (Singh et al. 2005). In addition, since PCR relies on the amplification of segments of

viral DNA rather than the culture of viable virus, PCR will yield a positive result several days after lesions no longer contain the infectious virus (Singh et al. 2005). HSV PCR is replacing viral culture as the gold standard for the diagnosis of genital herpes in women with active mucocutaneous lesions (Strick and Wald 2006).

2. Serologic tests indirectly test for HSV infection by detecting circulating antibodies produced by the host's immune system. This has the advantage over direct testing, because serologic testing can detect infected persons who are asymptomatic and would otherwise produce a false-negative result. Indirect serologic type-specific testing is useful in situations where viral culture/PCR returns negative, in patients with recurrent herpes, or when testing asymptomatic partners for HSV (CDC 2015a). Western blot detecting of HSV antibodies is the most specific test available to detect recurrent HSV lesions. It is currently considered the gold standard for detecting antibodies to HSV. One of the advantages of Western blot testing is that it can discriminate between types of HSV, HSV-1 and HSV-2. Western blot however is not widely available, very labor intensive, and time consuming.
   - Enzyme-linked immunosorbent assays (ELISA) are also commercially available to test for type-specific antibodies in patients' blood to HSV. ELISA technologies have been reported to have sensitivities from 97% to 100% and specificity as high as 98% in the detection of HSV-1 and HSV-2. Several of the current commercial ELISA tests for HSV-2 can yield a false positive at low values. In situations where a false-positive result is of consideration, Western blot should be performed to verify results (CDC 2015a). ELISA testing is available as point of care testing from capillary blood samples that can be done in the clinic.
     - Since type-specific testing can differentiate between HSV-1 and HSV-2, it is important to counsel patients on the significance of the result. HSV-1 can be acquired through orolabial transmission or through anogenital contact. The positive result of HSV-1 does not necessarily imply a sexually transmitted disease. However, HSV-2 is commonly transmitted through anogenital contact and is considered a sexually transmitted disease. Those who test positive for HSV-2 should be informed of their diagnosis, counseled on safe sex practices and risk of transmission to partners, and offered screening for other sexually transmitted diseases. It is recommended that patients who test positive for HSV-2 also be offered screening for HIV (CDC 2015a).

4.3 Treatment

Treatment for herpes infection can be divided into two separate arms. The first arm is aimed at treating the acute outbreak, either primary or recurrent. The second arm is aimed at preventing future outbreaks and decreasing the risk of transmission to a noninfected partner. Even without active lesions, there is asymptomatic viral shedding which puts partners at risk for transmission:

- The primary outbreak is typically treated with acyclovir 400 mg orally TID or 200 mg 5× a day for 7–10 days.
- Valacyclovir 1 g BID for 7–10 days or famciclovirr 250 mg TID ×7–10 days can also be used (Table 6).
- For recurrent outbreaks, treatment should be initiated during the prodromal phase or within the first 24 h of active outbreaks (Table 7). There are many treatment options available but typically acyclovir 400 mg po BID and 800 mg BID for 5 days are used.

Table 6 Primary treatment of HSV outbreak

Regimen	
Acyclovir 400 mg po TID ×7–10 days	Primary outbreak
Acyclovir 200 mg po five times daily ×7–10 days	Primary outbreak
Valacyclovir 1 g po BID ×7–10 days	Primary outbreak
Famciclovir 250 mg po TID 7–10 days	Primary outbreak

Table 7 Recurrent HSV outbreak Treatment

Regimen	Recurrent outbreak therapy
Acyclovir 400 mg po TID ×5 days	
Acyclovir 800 mg po BID ×5 days	
Acyclovir 800 mg po TID ×2 days	
Valacyclovir 500 mg po BID ×3 days	
Valacyclovir 1 g po ×5 days	
Famciclovir 125 mg po BID ×5 days	
Famciclovir 1 g po BID ×1 day	

Table 8 Suppressive HSV therapy

Regimen	Suppressive therapy
Acyclovir 400 mg po BID	
Valacyclovir 500 mg po daily	
Valacyclovir 1 g po daily	
Famiciclovir 250 mg po BID	

- Other regimens exist as well. Table 8 lists treatment options available for suppressive therapy to reduce viral shedding, transmission to partners, and future outbreaks.

5 Human Papillomavirus (HPV)

5.1 Background

Human papillomavirus (HPV) is a double-stranded DNA virus from the papillomavirus family that commonly infects the transitional zone in the cervix. HPV infection is the number one sexually transmitted disease in the United States with an estimate of more than 79 million persons infected with the virus (CDC 2013, 2015b). The majority of HPV infections will resolve on their own after 2 years. However, some infections are persistent and can significantly increase the risk for cervical and other cancers.

High-risk HPV plays an important role in cell cycle dysregulation. They commonly affect the oncoproteins E6 and E7 (Oh et al. 2005). When expressed, E6 oncoprotein binds to the P53 tumor suppressor gene and leads to its degradation. In a similar method, E7 binds to the RB tumor suppressor gene and inhibits its regulatory function. Seventy to 80% of cervical cancer is secondary to squamous cell carcinoma of the cervix. Studies have shown that nearly 100% of squamous cell carcinoma of the cervix is attributable to high-risk HPV (Saslow et al. 2012). HPV subtypes 16 and 18 are the most commonly encountered high-risk HPV subtypes. High-risk HPV refers to their oncogenic properties. Nearly 55–60% of cervical cancer appear to be caused by HPV 16 (Saslow et al. 2012).

It is well known that HPV is transmitted through sexual contact. Given that HPV is a virus, a healthy host's immune system will try to rid the body of the virus. For this reason, the majority of HPV infections are transient, lasting only 1–2 years. During the time of infection, it is possible to spread HPV to another sexual contact, thus, leading to the high prevalence of HPV in the population. If the HPV infection is not cleared from the body and persists, there is increased risk of developing cervical cancer or a precancerous lesion (Saslow et al. 2012).

The progression from normal cervical cytology to cervical cancer has been well studied. It is understood that the development of cervical cancer consists of precancerous lesions termed cervical intraepithelial neoplasia I, II, and III (CIN I, CIN II, CIN III). The progression of cervical cancer generally proceeds through each of these precancerous stages before malignant cells are formed. The fundamentals of cervical cancer screening are based on identifying abnormal cytology on the pap smear prior to the development of cervical cancer. With the advent of HPV testing in conjunction with cervical cytology testing, it is possible to identify those at high risk for development of cervical cancer and need shortened interval testing between cytologic examinations.

Currently, HPV screening has two primary uses. The first is in the setting of an equivocal cytology test (ASC-US). The presence of HPV will dictate the interval of screening and if further evaluation is necessary. In a patient who has a negative pap based on cytology, the presence of high-risk HPV will dictate whether the patient will need immediate

colposcopy vs. contesting in 1 year. The same can be said for when a pap smear shows a low-grade squamous intraepithelial lesion (LSIL). If the patient had been tested for HPV and the result is negative, co-testing in one tear is acceptable to evaluate for clearance of the abnormal cytology. However, in the setting when HPV status is unknown or the patient tests positive for high-risk HPV, then the patient needs further work-up with colposcopy (Saslow et al. 2012).

The second major use of HPV is for co-testing with cytology in patient's 30 years of age or older. Cytology with HPV testing can increase the interval between pap smears from 3 to 5 years (Saslow et al. 2012). For example, persons with a persistent HPV 16 infection for 1–2 years have a 20–30% risk of developing CIN III over the course of 5 years. If CIN III goes untreated, there is a 30% probability that it will develop into invasive cervical cancer over 30 years. In contrast, the risk of treated CIN III progressing to invasive cervical cancer over 30 years is quoted to be 1% (McCredie et al. 2008). Given that the median age of first intercourse in the United States is around 17 years of age and the high prevalence of HPV in the general population, one's risk of becoming infected with a high-risk HPV in their earlier years is significant:

- HPV testing in the setting of cytology allows for increased detection of high-risk patients, safely allows an increase in the interval between cytologic examination in low-risk individuals, and directs triaging of equivocal cytology results. In a reassuring study examining the change in lifetime risk for a 40-year-old woman undergoing cytology every 3 years versus contesting every 5 years showed a lifetime cervical cancer risk of 0.69% and 0.61%, respectively (Stout et al. 2008). Thus, showing the benefits is contesting.

5.2 Screening and Diagnosis

There are various methods for detecting HPV including cytology, hybrid capture, invader chemistry, PCR, and cytology. Even though various tests exist for detecting HPV, only two are FDA approved at this time (Hybrid Capture II and Cervista NPV):

- In 2014, the FDA approved the use of a HPV DNA test [cobas] for reflex or co-testing and primary screening (detects HPV types 16 or 18 and gives pooled results for 12 additional high-risk HPVs) as first-line primary screening test for use alone for women age 25 and older.
- The Hybrid Capture II relies on signal amplification using RNA probes directed against the DNA sequence of 13 high-risk HPV types (Nishino et al. 2011). The RNA will bind to the DNA from the HPV creating DNA-RNA hybrids which can be bound to a testing plate. This bound compound is then reacted with various substrates to emit light. At a given intensity, the test will be considered positive. Meta-analysis of the Hybrid Capture II sensitivities ranged from 92.5% to 95.6% (Nishino et al. 2011).
- The Cervista HPV HR and HPV 16/18 are signal amplification tests that rely on invader chemistry technology to detect the presence of HPV in cervical samples. The Cervista HPV HR was the first FDA approved test for detection of HPV in women. It can be used with specified cervical cytology collecting instruments such as the cervix brush and pipette and for use with the Thin Prep Pap Test PreservCyt Solution. The sensitivity for the Cervista when used according to FDA specification ranges from 92.8% to 100% (Nishino et al. 2011).
- Cervical cytology can detect morphologic effects of HPV– koilocytosis, nuclear hyperchromsia/enlargement, and cytoplasmic cavitation – but cannot differentiate high-risk from low-risk HPV.

5.3 Treatment

Currently there is no treatment for the HPV virus itself. There is only treatment for the HPV-related complications (CDC 2013, 2015b).

6 Conclusion

There is a high prevalence of sexually transmitted disease in the United States of America. While each sexually transmitted diseases is associated with its own unique signs and symptoms, they are often asymptomatic. Untreated sexually transmitted diseases can cause sequel such as infertility, hospitalization, cancer, sepsis, and death. It is the clinicians responsibility to know the indications for screening or testing patients for sexually transmitted disease. With today's technology, there are vast arrays of tests available to the clinician for the screening and diagnosing of sexually transmitted diseases. Each test has its own unique indications and may show superiority based on the pathogen and site being tested. It is imperative that the clinician is familiar with the tests available for diagnosis and the indications for each.

Proper screening and diagnosing of sexually transmitted diseases will lead to earlier detection, a reduction in time to treatment, and a reduction of overall complications from undiagnosed and untreated sexually transmitted infections.

7 Cross-References

- Benign Vulvar and Vaginal Pathology
- Common Problems in Adolescent Medicine
- Diagnosis and Treatment of Urinary Tract Infections
- Diagnosis and Treatment of Vulvovaginitis
- Fertility Sparing Treatment for Ovarian Cancer
- Gynecologic History and Examination of the Patient
- Management of Cervical Dysplasia
- Management of Chronic Recurrent Vulvovaginitis
- Management of Early-Stage and Locally Advanced Cervical Cancer
- Management of Intraepithelial Lesions of the Cervix
- Management of Metastatic and Recurrent Cervical Cancer
- Management of the Symptoms of Perimenopause
- Pelvic Inflammatory Disease and Other Upper Genital Infections

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