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Best Practices in Testing Adults and Adolescents for Chlamydia and Gonorrhea in the Emergency Department

An Information Paper

Introduction

The sexually transmitted infections (STIs) chlamydia and gonorrhea are the most commonly and second most commonly reported notifiable diseases in the United States (US), respectively, and can cause significant morbidity.[1] Emergency physicians (EPs) are on the front lines of diagnosis and treatment of these infections. EPs have a number of different strategies available to them for the purpose of diagnosis of these infections, and there is variability in terms of individual EP practice. The objective of this review is to identify the best strategies for diagnosing chlamydia and gonorrhea in adult and adolescent patients, taking into consideration patient, provider, and test characteristics.

Epidemiology

While chlamydia—caused by *Chlamydia trachomatis*—is usually asymptomatic, particularly in women, it can contribute to the development of pelvic inflammatory disease (PID), leading to infertility, pregnancy complications such as ectopic pregnancy, and chronic pelvic pain.[1] Furthermore, chlamydia infection can facilitate the transmission of human immunodeficiency virus (HIV) and be transmitted vertically to infants, leading to neonatal infections, such as ophthalmia neonatorum and pneumonia.[1] In 2016, over 1.5 million cases of this infection were reported, corresponding to a rate of nearly 500 cases per 100,000 population.[1] Rates of reported cases have increased over the last few years, though this may at least partially be due to increased screening as well as improved diagnosis and reporting.[1] Chlamydia is most prevalent in the South; among adults ages 20-24 years; among women (in whom it is twice as prevalent as compared to men); and among Black, American Indian/Alaska Native, and Native Hawaiian/Other Pacific Islander individuals.[1]

Like chlamydia, gonorrhea—caused by *Neisseria gonorrhoeae*—can contribute to the development of pelvic inflammatory disease (PID) and its complications, as well as the transmission of HIV. *N. gonorrhoeae* has progressively developed resistance to each of the antibiotics used to treat gonorrhea, rendering surveillance of antibiotic susceptibility increasingly important. In 2016, nearly 500,000 cases of this infection were reported, corresponding to a rate of almost 150 cases per 100,000 population.[1] Rates of reported cases have increased nearly 50 percent in the last decade after reaching a historic low in 2009, though again, this may in part be due to increased screening as well as improved diagnosis and reporting. Gonorrhea is most prevalent in the South, among men (likely reflecting increased transmission and/or detection and reporting among men who have sex with men), among young adults ages 20-24 years, and among Black, American Indian/Alaska Native, and Native Hawaiian/Other Pacific Islander individuals.

Indications for Testing

Infection with chlamydia or gonorrhea can manifest in a number of ways depending on the site of

exposure. Clinical symptoms compatible with urethritis or acute epididymitis in sexually active men and cervicitis or pelvic inflammatory disease in sexually active women should prompt testing for chlamydia and gonorrhea in the ED. In men, urethritis manifests as dysuria; urethral pruritus; or mucoid, mucopurulent, or purulent urethral discharge. A positive leukocyte esterase test or urine sediment with ≥10 white blood cells per high power field on first-void urine is further suggestive of urethritis in the appropriate clinical context.[2] Acute epididymitis is evidenced by testicular pain and tenderness to palpation of the epididymis. In women, cervicitis is marked by abnormal vaginal discharge or vaginal bleeding between menses (eg, following sexual intercourse) while pelvic inflammatory disease presents more prominently with lower abdominal pain, sometimes accompanied by fever. Right upper quadrant pain, nausea, vomiting, and fever in a sexually-active woman should prompt consideration of perihepatitis (Fitz-Hugh Curtis syndrome), often associated with *C. trachomatis* infection. Extragenital infections warranting testing for *N. gonorrhoeae* include pharyngitis in the setting of oral sexual exposure and proctitis following anal receptive intercourse. Disseminated gonococcal infection can present with purulent arthritis or a triad of tenosynovitis, dermatitis (particularly with pustular or vesiculopustular lesions), and polyarthralgias in young otherwise healthy adults, even in the absence of recent urogenital symptoms. In clinical settings where test results may not be readily available during the ED visit and patient follow-up is unlikely, it is reasonable to empirically treat for chlamydia and gonorrhea based on clinical suspicion.[2] In addition to chlamydia and gonorrhea, women presenting to the ED with cervicitis should also be evaluated for trichomoniasis and bacterial vaginosis. As best practice, all patients diagnosed with chlamydia or gonorrhea should be tested for other STIs, including HIV and syphilis.[2]

In some instances, patients with chlamydia or gonorrhea may have deceivingly mild or no symptoms at all, further complicating clinical diagnosis. The US Preventive Services Task Force (USPSTF) recommends screening for chlamydia and gonorrhea in all sexually active women aged 24 years or younger and in older women who are at increased risk for infection (new or multiple sex partners, a sex partner with concurrent partners, or a sex partner with a STI; inconsistent condom use among persons who are not in mutually monogamous relationships; previous or concurrent STI; exchanging sex for money or drugs).[3] Similar screening strategies in asymptomatic men are not recommended at this time. In the ED, recent sex partners of a patient diagnosed with chlamydia or gonorrhea should be tested and presumptively treated if they had sexual contact with the patient in the 60 days preceding the patient's onset of symptoms or diagnosis.[2] Decisions to screen for chlamydia and gonorrhea in sexual assault survivors should be made on an individual basis, particularly if empiric presumptive treatment of these infections is anticipated.[2]

Test-of-cure for chlamydia and gonorrhea is not necessary for uncomplicated urogenital or rectal infections.[2] In fact, *C. trachomatis* NAAT can remain positive for up to weeks after appropriate treatment owing to the persistence of nonviable organisms.[2] However, patients with pharyngeal gonorrhea treated with alternative regimens (eg, cefixime) should return 14 days after treatment for test-of-cure. All men and women treated for chlamydia or gonorrhea should ideally be retested three months after treatment per current CDC guidelines, largely due to the risk of reinfection from untreated sex partners or new partners in this patient population.[2] Persistent infection with gonorrhea due to cephalosporin treatment failure and thus additional testing for antibiotic susceptibility should be considered in patients who do not experience symptom resolution within three to five days of appropriate treatment with a cephalosporin and who have abstained from sexual contact since treatment.[2] However, most suspected treatment failures in the US are more likely to be related to re-infection.[3, 4]

Testing Modalities/Characteristics

The EP testing for chlamydia and gonorrhea must consider a number of factors in selecting the appropriate diagnostic modality, including accuracy, cost, ease, turnaround time, and invasiveness. Historically, culture was viewed as the gold standard to which other tests for both chlamydia and

gonorrhea were compared.[6] However, this modality presents some challenges in terms of maintaining the viability of organisms during transport and storage; additionally, culture methods for isolating *C. trachomatis* are hard to standardize, technically difficult, expensive, and insensitive. In response to these challenges, non-culture modalities were developed. The first of these were antigen detection tests, including enzyme immunoassays (EIAs) and direct fluorescent antibody (DFA) tests, for *C. trachomatis;* these employ fluorescein-conjugated monoclonal antibodies that bind to bacterial antigens. Next, nucleic acid hybridization tests were introduced; these detect either *C. trachomatis*- or *N. gonorrhoeae*- specific deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) sequences. While these tests were more convenient and—in remote settings—more reliable than their culture predecessor, they were insensitive, particularly for *C. trachomatis.* The subsequent development of nucleic acid amplification tests (NAATs), which amplify and detect *C. trachomatis*- or *N. gonorrhoeae*- specific DNA or RNA sequences, led to a convenient, reliable, and sensitive option for the diagnosis of chlamydia and gonorrhea.

Chlamydia

NAATs, including polymerase chain reaction (PCR), transcription-mediated amplification (TMA), and strand displacement amplification (SDA), are now considered the gold standard for diagnosing chlamydia. The US Preventive Services Task Force (USPSTF) evaluated ten fair-quality diagnostic accuracy studies and found that testing for chlamydia using NAATs had a sensitivity ranging from 86 to 100 percent and a specificity greater than 97 percent.[3] Among women, sites sampled for testing may include the vagina, cervix, or urine. A number of studies have demonstrated that vaginal and cervical swabs perform better than urine specimens in terms of sensitivity. Urine specimens may detect up to 10 percent fewer infections compared to vaginal and cervical swabs.[6] Some studies have shown that vaginal swabs perform better than cervical ones, though others have found them to be equivalent.[7] One study found that self-obtained vaginal (SOV) swabs performed as well as clinician-obtained ones and are preferred by women, suggesting that the means of obtaining samples should be taken into consideration in addition to the modality used.[7] Among men, sites sampled for testing may include the urethra and urine; urine specimens appear to be just as and perhaps slightly more sensitive than urethral swabs while also maximizing patient comfort.[6, 8] NAATs can also be used to evaluate for extragenital (eg, ophthalmic, oropharyngeal, rectal) infections; however, the FDA has not approved these for extragenital use, though testing validation under Clinical Laboratory Improvement Amendments (CLIA) is possible for individual laboratories.

Gonorrhea

As with chlamydia, NAATs are now considered the gold standard for diagnosing gonorrhea. The USPSTF found that testing for gonorrhea using NAATs had a sensitivity ranging from 90 to 100 percent and a specificity greater than 97 percent.[3] Like with chlamydia, among women, sites sampled for testing may include the vagina, cervix, or urine. In contrast, though, some NAATs (ie, PCR) demonstrate subpar performance with specimens other than cervical swabs.[9,10] Among men, as with chlamydia, sites sampled for testing may include the urethra and urine; urine specimens appear to be nearly equivalent to urethral swabs.[10] In addition, gram stain from a urethral swab is an option for confirming the diagnosis of gonorrhea in symptomatic men: its sensitivity and specificity are 95 and greater than 99 percent, respectively.[6] However, it is not thought to be sufficiently sensitive to rule the diagnosis out. Like with chlamydia, NAATs can be used to evaluate for extragenital infections, though again, they are not approved by the FDA for this use. Finally, while largely eclipsed by NAATs, culture is still useful as the test of choice in determining antibiotic susceptibility when resistance is suspected.

Conclusion/Recommendations

In summary, a number of testing modalities as well as sampling sites are available to the EP considering

the diagnoses of chlamydia and gonorrhea. The decision of which test and site to choose must be guided by the patient's presentation, clinical judgment, and test characteristics (and availability). In general, testing should involve NAATs, though gram stain is an option in symptomatic men in testing for gonorrhea. In women, testing for chlamydia should occur through vaginal (ideally) or cervical swabs rather than urine specimens, while testing for gonorrhea should occur through cervical (ideally) or vaginal swabs rather than urine specimens. In men, urine specimens are essentially equivalent to (and more acceptable to patients than) urethral swabs. Extragenital testing can also be done via NAATs. While NAATs are currently the gold standard, further research comparing NAAT modalities and brands against each other would be useful, as would the development of improved point of care testing.

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Reviewed by the Board of Directors – July 2019