29. Screening for Chlamydial Infection—*Including Ocular Prophylaxis in Newborns*

RECOMMENDATION

Routine screening for Chlamydia trachomatis infection is recommended for all sexually active female adolescents, high-risk pregnant women, and other asymptomatic women at high risk of infection (see *Clinical Intervention*). There is insufficient evidence to recommend for or against routine screening in asymptomatic men. Recommendations to screen selected high-risk male adolescents may be made on other grounds (see *Clinical Intervention*). Routine screening is not recommended for the general adult population. See Chapter 27 for recommendations regarding ocular prophylaxis to prevent ophthalmia neonatorum.

Burden of Suffering

Infection with *C. trachomatis* is the most common bacterial sexually transmitted disease (STD) in the U.S., affecting an estimated 4 million persons at a cost of $2.4 billion each year.[1,2] The medical consequences and costs of infection are greatest in women, who may develop urethritis, cervicitis, or pelvic inflammatory disease (PID; i.e., salpingitis or endometritis). Chlamydial infections are responsible for 25–50% of the 2.5 million cases of PID that are reported annually in the U.S.[3] PID is an important cause of infertility and ectopic pregnancy in American women and may lead to chronic pelvic pain. Data from other countries suggest that infection with chlamydia may be a cofactor in heterosexual transmission of HIV infection.[4] In men, chlamydia is responsible for 30–40% of the 4–6 million visits each year for nongonococcal urethritis and half of over 150,000 cases of acute epididymitis.[1]

Up to 25% of men and 70% of women with chlamydial infection are asymptomatic.[5] Immunologic surveys suggest that chlamydial infection increases the risk of infertility and ectopic pregnancy even in women who never develop clinical PID, most likely because the symptoms of salpingitis may be mild or nonspecific.[1] Asymptomatic infections in men and women also serve as an important reservoir for new infections.

Age is the strongest demographic predictor of chlamydial infection. Men and women under 25 account for the large majority of cases,[6] and prevalence of infection is highest among young women age 15–19. Although risk factors for chlamydia are similar to those for other STDs, chlamydia is distinct in that the prevalence of infection is substantial (>5%) among sexually active female adolescents in general, regardless of race, place of residence, or socioeconomic status.[1,7] For example, infection was present in 5–8% of North American female college students at student health clinics[8,9] and 8–26% of teenage girls attending adolescent clinics.[10,11] The high risk in young women probably reflects both behavioral and physiologic factors (increased exposure of cervical columnar epithelium in young women).[12] Other important risk factors for chlamydial infection include having multiple sex partners, a new sex partner, or an infected sex partner; inconsistent use of barrier contraceptives; and cervical ectopy on examination.[1,7,13–18] Among 1,800 women ages 15–34 screened in a health maintenance organization, marital status was the single strongest predictor of infection: prevalence was less than 1% among married women, 7% among single women, and 3–4% among those divorced or living as married.[15] Chlamydial infection is more prevalent among blacks than among whites or Hispanics.[15,19] In routine screening, women with vaginal discharge, cervicitis, or cervical friability (i.e., bleeding induced by swab) were more likely to be infected.[7,15] Chlamydial infection is common among women with other STDs, incarcerated women,[20] and women seeking abortions.[21] In high-risk urban communities, chlamydia was detected in 6–11% of asymptomatic, sexually active male adolescents.[22,23]

The overall prevalence of chlamydial infection among pregnant women in the U.S. is estimated to be about 5%, but it varies widely (0–37%), depending on age and other risk factors.[24] Many sites serving younger women and high-risk urban communities have reported a substantially higher prevalence of infection (10–25%).[25,26] Infection during pregnancy increases the risk of endometritis, both after delivery and after elective abortion.[1,27] Each year more than 155,000 infants are born to chlamydia-infected mothers, and the organism is transmitted to the fetus in over half of deliveries.[24] Neonatal infection can result in ophthalmia neonatorum and pneumonia.

Accuracy of Screening Tests

The most specific test for chlamydial infection in asymptomatic persons is culture. Urethral and endocervical cultures have been estimated to have a sensitivity of about 70–90% and a specificity of 100%.[1,22] In addition to its variable sensitivity, culture is expensive, not uniformly available, requires careful handling of specimens, and takes 3–7 days for results. In one study,

one fourth of women with positive cultures did not return for therapy.[28] In men, screening with culture requires obtaining specimens with urethral swabs, which is unacceptable to many asymptomatic men.[22]

A variety of nonculture tests are now available, offering the advantages of easier handling and processing, lower costs, wider availability, and more timely results. Commercially available tests employ enzyme immunoassay (EIA), direct fluorescent antibody (DFA), DNA probe, polymerase chain reaction (PCR), or solid-phase colorimetric assays[28] to detect chlamydia in urethral or cervical specimens. Tests using ligase chain reaction (LCR) are awaiting Food and Drug Administration (FDA) approval.[29] Of these tests, EIA and DFA tests have been most widely evaluated, with reported sensitivities of 70–90% and high specificity (97–99%).[1] False-positive EIA results may result from cross-reaction with other vaginal flora or urinary pathogens, but confirmation of positive tests using blocking antibody increases specificity to close to 100%. Studies in STD clinics indicate that DNA probe, PCR, and LCR can each be very sensitive and specific (>95%).[30,31] Sensitivity of commercial PCR and DNA probe kits was significantly lower (60–75%) in some studies,[32,33] however, and the performance of these assays for screening asymptomatic patients needs further evaluation. The arrival of competitively priced, commercial kits is likely to make these increasingly popular alternatives to chlamydia culture.

The ability to detect chlamydial infection in centrifuged, first-void urine specimens may make screening asymptomatic men more feasible.[22–24] Urine dipsticks can detect leukocyte-esterase (LE) activity, an indicator of urethritis or upper urinary infections. However, the sensitivity of LE testing for chlamydial infection is variable (40–100%),[1] and the low predictive value of LE in asymptomatic young men (11% in one study[22]) necessitates use of confirmatory tests. Testing urine specimens with EIA is more sensitive (77–91%) and specific (97–100%), but it substantially increases the cost per confirmed case.[22,34] PCR and LCR assays appear to have the highest sensitivity and specificity (95–99%) for chlamydia using urine specimens.[23,29,35] A recent study reported that LCR assays of urine were also very sensitive and specific for chlamydial infection in women (94% and 99.9%, respectively).[36]

Even with highly specific tests, the likelihood that a positive result indicates true infection varies with the prevalence of infection in the population being screened. Assuming a sensitivity of 80% and specificity of 98%, the positive predictive value of a test will range from 82% when prevalence of chlamydia is high (10%), to only 45% when prevalence is low (2%). As a result, independent confirmation of positive results from some nonculture tests may be necessary to prevent false-positive results in low-risk patients.

In prospective studies of screening in low-risk populations, risk scores based on age, other risk factors, and findings on physical examination successfully identified a subpopulation of high-risk women (prevalence 6% or higher) who accounted for the large majority of all infections.[15,16,37]

Effectiveness of Early Detection

Early detection of chlamydial infections in asymptomatic persons permits initiation of antibiotic therapy to eradicate infection. The benefits of detecting and treating asymptomatic infection in pregnancy have been demonstrated in several large cohort studies of high-risk women screened at the first prenatal visit.[26,38] Infected women who received erythromycin had significantly lower rates of preterm delivery, rupture of membranes, and low birth weight compared to infected women who were untreated or treatment failures. In one study, treatment was associated with lower perinatal mortality among children.[26] Some of the benefit may have been due to effects of erythromycin on pathogens other than *Chlamydia* or underlying differences between treated and untreated women.

Eradication of asymptomatic infection is also likely to reduce the complications of chlamydial infection in nonpregnant women. Proving a benefit on long-term se-quelae of infection (e.g., infertility and ectopic pregnancy) is difficult, but a recent trial in a large health maintenance organization demonstrated that at-risk women randomized to receive routine chlamydia screening were less than half as likely to develop PID over the next year (1% vs. 2.2%).[37] Hospitalizations for PID also declined in Sweden in association with increased chlamydia screening, but other changes in sexual behavior are likely to have contributed to this trend.[39] Treatment effectively eradicates chlamydial infection, but it has traditionally required an extended course of medication. A 7-day course of tetracycline or doxycycline results in a short-term cure in 92–100% of women and 97–100% of men.[1] Single-dose therapy with azithromycin is as effective as doxycycline and may be a suitable alternative when noncompliance is a concern.[40] The benefits of early detection are limited by high rates of reinfection or treatment failure in some populations.[1] In follow-up studies of adolescent women treated for chlamydia, 26–39% are infected 2–5 years later.[41,42] Treatment failures are usually due to failure to treat sex partners, noncompliance with therapy, or reinfection. Referral of sex partners of cases is important, since up to one third of male partners, and a majority of female partners, are infected.[5]

Chlamydia may cause epididymitis, but serious complications of chlamydial infection are uncommon in men. Although screening and treating high-risk young men has the potential to reduce the incidence of chlamydia, the impact of routine screening in men has not been examined

prospectively, or compared to the current strategy of screening women and treating male partners. A variety of other factors will influence whether screening men will significantly reduce the incidence of new infections: duration of asymptomatic period, rates of transmission from asymptomatic men to their female partners, compliance with treatment, and rates of re-infection in young men.

Ocular Prophylaxis in Newborns

Between 20% and 50% of all infants born to infected mothers develop chlamydial conjunctivitis, but there is conflicting evidence of the benefit of universal ocular prophylaxis with topical antibiotics (erythromycin, tetracycline, or silver nitrate) after birth to reduce the incidence of chlamydial ophthalmia neonatorum.[43–45] In a recent trial in Kenya, where maternal chlamydial infection is common, povidone-iodine was significantly more effective than erythromycin or silver nitrate for preventing chlamydial conjunctivitis in newborns.[46] The failure rate of ocular prophylaxis for chlamydia has been estimated to be 7–19%, and chlamydial ophthalmia (unlike gonococcal ophthalmia) is rarely associated with serious ocular complications.[45] In a trial among infants born to low-risk American women, prophylaxis with silver nitrate or erythromycin reduced the incidence of conjunctivitis compared to placebo (8–9% vs. 15%); regardless of treatment, however, most cases were mild and due to organisms other than chlamydia.[47]

Recommendations of Other Groups

Screening for chlamydia in asymptomatic sexually active female adolescents (under 20 years old), and in other women with risk factors for infection, is recommended by the Centers for Disease Control and Prevention (CDC),[1] the American College of Obstetricians and Gynecologists (ACOG),[48] the American Academy of Pediatrics (AAP),[49] Bright Futures,[50] the American Medical Association,[51] the American Academy of Family Physicians (AAFP),[52] and the Canadian Task Force for the Periodic Health Examination (CTF);[53] AAFP recommendations are under review. Some of these organizations also make these recommendations for adolescent males and young men at high risk. Risk factors cited by various organizations include age under 25, new or multiple sex partners in the past 3 months, inconsistent use of barrier contraception, the presence of mucopurulent cervicitis or cervical friability, the diagnosis of other STDs, and others. An expert panel convened in 1994 by the Institute of Medicine, National Academy of Sciences, is developing recommendations for public health strategies to control STDs, including chlamydia.

The CTF recommends that all pregnant women be screened for asymptomatic chlamydial infection.[53] Both ACOG and CDC recommend screening with chlamydial culture in high-risk pregnant women (including those under age 25), at the initial prenatal visit and/or in the third trimester.[1,48] No major organization recommends routine screening of the general population. The CDC, CTF, AAP, and AAFP all recommend routine ocular antibiotic prophylaxis for all newborns, primarily to prevent ophthalmia neonatorum due to *Neisseria gonorrhoeae* rather than *Chlamydia* (see Chapter 27).[1,45,49,52] Ocular prophylaxis is required by law in most states in the U.S.

Discussion

The substantial long-term morbidity from chlamydia in women, the high prevalence of asymptomatic infection, and the availability of reliable screening tests and effective treatments all suggest that screening for asymptomatic chlamydial infection may be a useful strategy. There is now preliminary evidence from one trial that screening high-risk asymptomatic, nonpregnant women can reduce the incidence of PID. Screening and treatment of infected women and their partners is also likely to reduce the incidence of new infections, although conclusive proof of this is not available. While high-risk sexual behavior is an important determinant of risk of chlamydial infection, the generally high prevalence of chlamydia among sexually active female adolescents supports routine screening in this population.[7]

The optimal criteria for screening other women depend on the local burden of disease and resources available for screening. Risk of infection depends on both individual sexual behavior and the prevalence of chlamydia in the community. Where the prevalence of infection is documented to be low (<5%), targeting screening to women with multiple risk factors for infection may be most efficient. Because self-reported sexual history is often an unreliable indicator of risk, however, broader screening of young women may be preferable in practices or communities where chlamydia is highly prevalent.

There is fair evidence that treatment of chlamydial infection during pregnancy is associated with improved outcomes for both infants and mothers. Due to the low prevalence of infection in women who are older or married, universal screening is not indicated in pregnancy. Since the primary benefit of treatment in pregnancy is to prevent perinatal and postpartum complications, screening high-risk women in the third trimester is likely to be effective and reduce the opportunity for reinfection prior to delivery. Although ocular prophylaxis appears to reduce the risk of chlamydial ophthalmia neonatorum, screening and treating high-risk mothers

may be a more effective means of preventing chlamydial infections in newborn infants.

Screening is less likely to benefit asymptomatic men, but screening young men using urine-based tests (LE, EIA, or PCR) may be a useful strategy to prevent spread of infection in communities where chlamydia is common. Whether routine screening in men is effective in reducing the incidence of chlamydial infection deserves further study, however.

Nonculture methods are appropriate alternatives to cell culture for diagnosis of infection. The choice of optimal testing strategy will depend on available resources, the prevalence of chlamydia, and the potential adverse consequences of false-positive diagnoses. Newer methods such as PCR or LCR are likely to offer advantages due to improved sensitivity and specificity; further evaluations of new commercial test kits are needed in asymptomatic populations before specific recommendations can be made.

Cost-effectiveness analyses have concluded that screening for chlamydia with nonculture tests is cost-effective during routine gynecologic visits[54–56] and during pregnancy[57] when prevalence of infection exceeds 6–8%. Others have suggested that screening is cost-effective at even lower prevalence.[13] Screening asymptomatic adolescent males with urine-based tests was calculated to be cost-saving, primarily by reducing infections in female partners, but has not been compared to the current strategy of screening women.[34]

CLINICAL INTERVENTION

Routine screening for asymptomatic infection with *Chlamydia trachomatis* during pelvic examination is recommended for all sexually active female adolescents and for other women at high risk for chlamydial infection ("B" recommendation). Patient characteristics associated with a higher prevalence of infection include: history of prior STD, new or multiple sex partners, age under 25, inconsistent use of barrier contraceptives, cervical ectopy, and being unmarried. Actual risk will depend on number of risk factors and local epidemiology of chlamydial infection. Clinicians may wish to consult local public health authorities for guidance in identifying high-risk populations within their community. Algorithms to identify high-risk women have been published.[15,16] In clinical settings where the prevalence of infection is known to be high (e.g., some urban family planning clinics), routine screening of all women is appropriate. Clinicians should remain alert for findings suggestive of chlamydial infection (e.g., mucopurulent discharge, cervical erythema, or cervical friability) during pelvic examination of asymptomatic women.

Pregnant women at high risk of infection (including age under 25) should be tested for chlamydia ("B" recommendation). The optimal tim-

ing of screening in pregnancy is uncertain. There is insufficient evidence to recommend for or against screening all women during pregnancy ("C" recommendation).

There is insufficient evidence to recommend for or against routine screening in high-risk men ("C" recommendation). In clinical settings where asymptomatic infection is highly prevalent in men (e.g., urban adolescent clinics), screening sexually active young men may be recommended on other grounds, including the potential to prevent transmission to uninfected sex partners. Routine screening for chlamydia is not recommended in the general population of low-risk adults ("D" recommendation).

In women, endocervical specimens should be obtained for cell culture or nonculture assays. Verification of positive nonculture results may be necessary, depending on the underlying risk in the patient and potential adverse consequences of a false-positive result. The choice of screening test for asymptomatic men is left to clinical discretion. Urine LE dipstick is much less expensive than urine assays using EIA, PCR, or LCR, but it is also less sensitive and specific for asymptomatic chlamydial infection. The optimal frequency of testing has not been determined for women or men and is left to clinical discretion.

Routine ocular antibiotic prophylaxis with silver nitrate, erythromycin, or tetracycline is recommended for all newborn infants to prevent ophthalmia neonatorum due to gonorrhea and is required by law in most states (see Chapter 27). There is insufficient evidence to recommend for or against universal ocular prophylaxis of newborns solely for the prevention of chlamydial conjunctivitis ("C" recommendation).

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