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Chlamydia trachomatis Infection: Screening and Management

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Abstract

Objective—To review current criteria and rationale for *Chlamydia trachomatis* screening, testing methods, and treatment of infection.

Methods—Review of the literature.

Results—*C. trachomatis* urogenital infections are an important public health problem. Screening for *C. trachomatis* in women age 25 and younger and men and women of any age at increased risk allows for the early treatment of disease, avoiding morbidity such as pelvic inflammatory disease, ectopic pregnancy, and chronic pelvic pain, and reducing health care costs.

Conclusion—Current screening recommendations are not being implemented satisfactorily. Home-based methods of screening are acceptable and may improve universal screening rates.

C*hlamydia trachomatis* infection is the most commonly reported sexually transmitted infection (STI) in the United States, with approximately 2.8 million infections reported annually [1] and an estimated prevalence rate of 457.6 cases per 100,000 population [2]. The vast majority of chlamydial infections are asymptomatic. Untreated chlamydial infection can cause serious sequelae, including pelvic inflammatory disease (PID) [3,4], which can lead to ectopic pregnancy, tubal infertility, and chronic pelvic pain [5–9]. Chlamydial infection in pregnancy is associated with an increased risk of preterm labor, low birth weight, and perinatal mortality [10]. Chlamydial infection imposes a substantial cost burden on the health care system [11–13].

Multiple risk factors for *C. trachomatis* infection have been identified. Most infections occur in sexually active individuals younger than 26 years of age, and especially among those 16 to 19 years of age. Minorities are affected disproportionally, as are those of low socioeconomic status [14]. Other risk factors include cervical ectopy [15], new or multiple sex partners, unprotected sex, inconsistent use of a barrier method, and early coitarche. Men in the military under age 30, men in the prison system, as well as males or females in juvenile detention are all at increased risk [16,17]. In addition, risk is markedly increased in

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men and women with *Neisseria gonorrhoeae* or *C. trachomatis* infection within the last 12 months [18].

Screening for chlamydia is recommended in several population subgroups. However, many of those at risk do not receive screening. This article will review current screening recommendations, screening tests, barriers to screening, and management of infection.

Evidence for Screening

Two randomized controlled trials (RCTs) have been performed that show benefit of chlamydia screening. In 1996, Scholes and colleagues [19] randomized women in a Seattle HMO at high risk for chlamydial infection to routine screening and treatment or usual care. Surveys were sent to women aged 18 to 34 and risk was determined based on their responses to the survey questions. Among eligible women, screening and treatment reduced the risk of subsequent PID by 50% after 1 year of follow-up. A limitation of the trial was that the researchers concentrated on making telephone reminder calls to nonresponders assigned to the screening group. This preferential contact may introduce a selection and differential response bias. There was also some imbalance in the 2 groups in terms of number of sexual partners in the past 12 months; however, multivariable adjustment did not alter the effect estimate.

Based on this trial and the weight of the scientific evidence, in 2001 the US Preventive Services Task Force (USPSTF) recommended screening for chlamydial infection in all sexually active, nonpregnant young women ages 25 and younger and in older nonpregnant women at increased risk (grade A recommendation) [20]. In its 2007 update, the USPSTF found 1 additional RCT [21] addressing the effectiveness of screening for chlamydial infection among nonpregnant women at increased risk. Ostergaard and colleagues [21] conducted a cluster randomized trial involving high school students in a Danish county. Students in the intervention schools were offered home-based screening while students in control schools were provided with educational information and encouraged to visit their physician for a free screening. The intervention was associated with a 50% reduced risk of PID (4.2% vs. 2.1%, $P = 0.045$) at 1 year. In 2007, the USPSTF changed the recommended age for testing to 24 years and younger [22].

More recently, the POPI (Prevention Of Pelvic Infection) trial [23] found discrepant results and added controversy to the issue of chlamydial infection screening. This RCT enrolled 2259 sexually active women in London who completed a baseline questionnaire and collected self-taken vaginal swabs at enrollment. Baseline rates of chlamydial infection were similar in both groups. Women in the intervention group underwent immediate testing and treatment (when positive) while among the control group samples were frozen and tested 1 year later. The rate of PID was found to be 1.3% in the screened group compared to 1.9% in the control group (risk ratio 0.65, 95% confidence interval [CI] 0.34–1.22) [23]. The study's major strengths include a large sample size and a 94% follow-up rate in a high-risk population. Unfortunately, the incidence of PID upon which the authors powered their study was 2% to 3%, resulting in an underpowered study. In addition, this study is based on prevalent chlamydial infections rather than incident infections. The authors concluded that

previous studies may have overestimated the effectiveness of screening for chlamydial infection to prevent PID. However, the relatively wide confidence interval demonstrates the lack of precision of their effect estimate.

A community-based chlamydia screening trial, The Australian Chlamydia Control Effectiveness Pilot (ACCEPt) [24], is currently underway to determine if chlamydia testing reduces the burden of infection in the Australian population. This cluster RCT is randomizing clinics by geography into control or intervention groups and is testing the feasibility, acceptability, efficacy and cost-effectiveness of annual chlamydia testing among 16- to 29-year-olds.

Screening Tests

Multiple tests have been used for the diagnosis of urogenital *C. trachomatis* infections, including nucleic acid amplification tests (NAATs), direct immunofluorescence, enzyme immunoassays, and nucleic acid hybridization tests (Table 1) [25,26]. Originally, cell culture was considered to be the gold standard because of its superior specificity and ability to detect a very small number of chlamydial organisms; however, NAATs are the most sensitive and specific tests for detecting chlamydial infections and have become the standard diagnostic and screening test [27,28].

The availability of NAATs has allowed for expansion in methods of screening. Diagnosis of urogenital infections in females can be made by testing urine or collecting vaginal or endocervical swabs. In a large cross-sectional study comparing first-void urine, self-collected vaginal swabs, and endocervical specimen, the vaginal swab had the highest detection rate of positive tests (86%) and was also most preferred by patients [29]. The endocervical specimen alone detected 65% of positive specimens, and first-void urine detected 72%. Other studies have confirmed both a high sensitivity and specificity as well as a high correlation between self-collected vaginal swabs performed at home and vaginal specimens collected by practitioners in a clinic setting [30,31].

In an analysis by Blake et al comparing different screening strategies (endocervical DNA probes, self-obtained vaginal swab, first-void urine), self-obtained vaginal swabs were found to have the highest sensitivity (97.2%) and prevented 17 additional cases per 10,000 women compared with first-void urine [32]. An additional 88 cases per 10,000 women screened would be identified by using the vaginal swab method compared with standard office-based screening with an endocervical DNA probe. Additionally, cost savings of over $40,000 per 10,000 women screened were a result of decreased treatment for PID, decreased infertility treatments, and decreased treatment of chronic pelvic pain [32].

Polymerase chain reaction testing of the residual fluid obtained during routine Pap testing using the liquid-based cytology samples has shown high CT detection rates [33]. Urine and endocervical samples appear to be equivalent in detection of CT in pregnant women [34].

Screening Recommendations

Recommendations for screening depend on gender and pregnancy status and are summarized in Table 2. Current recommendations from the CDC as well as the American College of Obstetricians and Gynecologists (ACOG) are to screen all sexually active females 25 years of age and younger [1,35,36]. The USPSTF recommends screening all sexually active women 24 years of age and younger. Women older than 24 years should be screened only if they have risk factors for infection such as multiple partners, inconsistent or nonuse use of a barrier method, being institutionalized, or members of the military under age 30 [37]. The UK's National Chlamydia Screening Programme recommends annual screening for all sexually active individuals 24 years of age and younger [38]. NAAT is the testing method of choice for men and women. In men, urethral swab or first void samples are recommend [37,39], while in women the CDC recommends a vaginal swab [25].

Pregnant Women

The CDC recommends that all pregnant women be screened for chlamydia [1,35]. The USTPF, ACOG, and the American Academy of Family Physicians (AAFP) recommend screening in pregnant women 24 years of age and younger, as well as women of any age who are deemed high risk. High risk is defined as less than 25 years of age or have new or multiple sexual partners [16,36,40]. ACOG also recommends rescreening of pregnant women in their third trimester [36]. For pregnant patients with a positive result on screening, a test of cure should be performed to ensure clearance of the infection. A test of cure is not the same as rescreening. Rescreening typically is an assessment for reinfection rather than incomplete or ineffective treatment. Occasionally, rescreening may detect persistent infection, but most infections at rescreening are reinfections, either from an infected new partner or an untreated prior partner. A test of cure is typically performed a week or two following completion of therapy, while rescreening is carried out several months later [38,41].

Men

Due to the differences in prevalence of infection in men and women, neither the CDC nor the USPSTF recommend routine screening of male patients. However, both groups endorse screening those deemed at higher risk, such as men with multiple sexual partners, those in juvenile facilities, and those in the military younger than 30 years of age. Patients with HIV should receive testing at the time of diagnosis and then annually. Sexually active men who have sex with men (MSM) should receive anorectal STD screening including screening for chlamydia at least annually.

Non-urogenital Infections

Though the genitalia are infected most commonly, other orifices can also be infected. Rectal chlamydial infection screening should be performed for MSM who have had receptive anal intercourse in the preceding year. Urethral chlamydia screening should be performed for MSM with insertive intercourse during the past year. Currently, pharyngeal screening of chlamydia is not recommended by the CDC for MSM; however, they do recommend pharyngeal screening for *N. gonorrhoeae* in this population [35].

Barriers to Screening

Despite screening for chlamydial infection being a Healthcare Effectiveness Data and Information Set (HEDIS) measure for over a decade, poor screening rates persist. In an analysis of preventative care visits involving a Pap smear or pelvic exam for women aged 15 to 25, chlamydia screening was performed at only 18% of visits [42]. This study may overestimate the percentage not being screened, as the investigators did not control for "sexually active" patients; however, the low overall screening rates imply there are significant opportunities for screening being missed. According to HEDIS data, the annual screening rates for sexually active women from age 16 to 24 range from 42% of patients in commercial PPOs to 58% of Medicaid participants [43]. While these rates have increased from previous years, a large portion of women are still not being screened [44].

Lack of screening has been attributed to both patient and provider barriers to participation. In a survey of primary care physicians, only 31% of respondents report they would screen asymptomatic, sexually active women aged 15 to 25 at a routine visit. Those less likely to screen were male providers, those with perception that incidence of chlamydial infection is low, solo practitioners, practitioners in rural settings and practitioners with few minority patients [45]. Patients are less likely to pursue screening when they lack knowledge of the asymptomatic nature and possible long-term morbidity of the infection. Others avoid screening due to the stigma of screening or receiving a positive diagnosis. Additional barriers include inability to pay for the test and the time associated with screening [44,46].

In 2 studies of participants in the Contraceptive CHOICE Project, which provided no-cost contraception to 9256 women in the St. Louis region, women were offered STI screening at the time of their annual follow-up. In the first study, clinic-based or home-based self-collected vaginal swabs were offered. Women who chose home-based testing were more likely to complete testing compared with those who chose clinic testing (64.6% vs. 31.6%) [47]. Minority race/ethnicity, low socio-economic status, and lack of insurance were associated with decreased completion of screening despite the fact that there was no cost for testing. In the second study, women consenting to STI screening were randomized to vaginal swabs self-collected at home or collected in the clinic. Women in the home-based self-collection group were more likely to complete screening compared with those in the clinic group (56.3% vs. 32.9%, RR 1.7, 95% CI. 1.4–2.0). Among those who did not complete the screening, the most cited reasons were "forgot" and "not enough time" [48].

Interventions to overcome barriers to screening have been investigated. Educational outreach and a financial incentive to increase general practices' contribution to chlamydia screening in 2 boroughs of South-East London with high prevalence of sexually transmitted infections led to a significant increase in the number of tests performed [49]. In Norway, Klovstad and colleagues conducted an RCT that studied whether screening with information and home sampling would result in more men and women aged 18–25 years being tested, diagnosed and treated for genital *C. trachomatis* in the 3 months following the intervention [50]. Young adults (n = 1000)received an invitation by mail with chlamydia information and a mail-back sampling kit. The control group consisted of 31,000 men and women who received no intervention and continued with usual care. In the intervention group, 16.5%

were tested for chlamydial infection versus 3.4% in the control group. The intervention group was 2–3 times more likely to be diagnosed and treated for chlamydial infection than those not receiving the intervention [50].

As mentioned, noninvasive collection methods have allowed for screening to take place outside of the clinic setting and without a physical examination by a clinician [56]. Multiple studies have shown that home collection of both urine and vaginal swabs in male and females increases the percentage of individuals screened compared with clinic-based visits [48,51,52]. Women are more likely to choose home-based screening when given a choice between clinic- and home-based screening [48]. In one study, 51% of the teens who screened positive with vaginal swabs in a home-collection kit reported that they probably would not have undergone screening in a clinic setting [53]. Internet recruitment with self-collected vaginal swabs mailed to laboratories has been found to be acceptable to patients as well [54,55]. First-void urine is preferred for males secondary to its noninvasive nature and high sensitivity and specificity (90%–97% and 99%, respectively) [26,56,57].

Management

Prompt treatment of individuals testing positive and exposed partners is necessary to minimize morbidity of the disease and prevent disease transmission. The CDC-recommended treatment regimens are azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days [35]. Debate about whether doxycycline or azithromycin is preferable as a treatment was addressed in a 2002 meta-analysis by Lau et al, who found comparable cure rates [58]. A more recent meta-analysis by Hocking and colleagues revealed a marginal yet statistically significant advantage of doxycycline over azithromycin [59]. Various alternate regimens with erythromycin and fluoroquinolones are outlined by the CDC for individuals unable to tolerate the preferred regimens [35] (Table 3).

Treatment should be given to every sexual contact the patient had up to 60 days before symptom onset or diagnosis. If their last sexual contact was more than 60 days prior to symptoms or diagnosis, then their last sexual contact should be treated. The provision of additional prescriptions and medication instructions for the patient to give to their sexual partner or partners without requiring them to be seen is the cornerstone of Expedited Partner Therapy (EPT). EPT increases the percentage of exposed partners who are treated [60,61]. Despite being recognized as safe and condoned by ACOG [62] and the CDC, its legality is unclear in some states, limiting implementation. As of July 2013, EPT has been specifically legalized in 34 states and is explicitly illegal in 6 states (FL, KY, MI, OH, OK, and WV). In 10 states, there is ambiguity, because there are no specific laws allowing provision of prescriptions for a patient who has not been evaluated by a clinician. The CDC provides up to date information about the legal status of EPT on their website (www.cdc.gov/std/ept/legal/default.htm).

A test of cure is not necessary in non-pregnant females and males because treatment with azithromycin or doxycycline is so effective. However, reinfection is common. Therefore, the CDC and NCSP recommend that individuals testing positive undergo repeat testing in 3 months to ensure they have not been reinfected, which is especially important when the

sexual partner is not treated. Pregnant females should undergo a test of cure after treatment because of the significant risks associated with neonatal CT infection. In order to prevent reinfection, individuals should abstain from sexual intercourse until 1 week after treatment with azithromycin or upon completion of the 7-day doxycycline regimen. Given that abstinence is not always a realistic goal, consistent condom use should be encouraged until all partners are treated as well [35,38]. Due to the increased susceptibility of HIV acquisition in the setting of positive chlamydia testing, screening for HIV should occur concomitantly [63].

Conclusion

In light of the relatively high prevalence of chlamydial infections and the underutilization of screening, increased efforts to promote screening can have a significant public health impact. Given the potential to reduce the associate adverse outcomes of PID, chronic pelvic pain and infertility, the authors recommend that all sexually active females 25 years of age or younger should receive annual screening. Annual screening is also recommended in sexually active females 26 years of age or older with risk factors for chlamydial infection or when screening in a geographical region with a high chlamydia prevalence. Women should be given the option of home-based screening with self-collected vaginal swabs, based on increased compliance, patient preference, and potential for cost savings. Given the morbid consequences of neonatal chlamydial infections, pregnant women should be screened upon initiation of prenatal care and rescreened in the third trimester. Data are lacking to support routine chlamydia screening in all males; however, MSM should be screened annually. Efforts should include education, decreasing barriers to care, promotion of routine screening including home-based screening and self-collected vaginal swabs in women, and effective and expeditious treatment of infected individuals and their partners including EPT. We believe that improvements in screening rates and increased access to effective treatment will have a large net gain in terms of reducing pain, suffering, and health care costs.

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Table 1

Sensitivities and Specificities of Screening Tests for *Chlamydia trachomatis* Infections

	Women [26,32]		Men [56]	
	Sensitivity	**Specificity**	**Sensitivity**	**Specificity**
NAAT				
Vaginal	97.2%	99.5%		
Endocervical	91.7%	98.3%		
Urine	91.7%	99.3%	90–97%	99%
DNA probe	68.8%	99.8%	65–83%	99%
DFA	80–85%	99%	80–85%	99%
EIA	60–85%	99%	53%	99–100%
Cell culture	50–85%	100%	70–85%	100%

DFA = direct fluorescence assay; EIA = enzyme immunoassay; NAAT = nucleic acid amplification test.

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Table 2

Recommendations for *Chlamydia trachomatis* Screening by Major Organizations

Cohort	AAFP [40]	ACOG [36]	CDC [1,35]	NCSP [38]	USPSTF [37]
Sexually active nonpregnant women	Annual screening ≤ 24 years of age and others at increased risk	Annual screening ≤ 25 years of age and others at increased risk	Annual screening ≤ 25 years of age and others at increased risk	At least annual screening and with change of sexual partner ≤ 24 years of age and more often at assessment of clinician	Annual screening ≤ 24 years of age and others at increased risk
Pregnant women	Screen women ≤ 24 years of age and others at increased risk	Screen women ≤ 24 years of age and others at increased risk	Screen all; retesting for all positive or high risk	No specific recommendation	Screen women ≤ 24 years of age and others at increased risk
WSW	No specific recommendation	No specific recommendation	Screen as sexually active nonpregnant women	No specific recommendation	
Men	"Current evidence is insufficient to assess the balance of benefits and harms screening for chlamydial infection for men"	Consider screening young adult males in settings associated with high prevalence of chlamydia	Screen men in high-prevalence settings (adolescent clinics, correctional facilities, STI clinics)	At least annual screening and with change of sexual partner, ≤ 24 years of age, and more often at assessment of clinician	"No recommendation due to insufficient evidence"
MSM	No specific recommendation	No specific recommendation	Annual urine NAAT for those having insertive intercourse and rectal swab NAAT for those having receptive anal intercourse	No specific recommendation	No specific recommendation
High-risk groups	No specific recommendation	High-prevalence areas, those entering detention facility, those who exchange sex for drugs or money	High-prevalence areas, those entering detention or correctional facility ≤ 35 years of age	Defined at discretion of clinician	History of chlamydia or other STI, new or multiple sexual partners, inconsistent condom use, sex work
Retesting	No specific recommendation	Retesting of all pregnant women in the 3rd trimester	Retesting for all positive pregnant women in 3rd trimester	Test of cure not necessary unless treated with erythromycin	No specific recommendation

AAFP = American Academy of Family Physicians; ACOG = American College of Obstetricians & Gynecologists; CDC = Centers for Disease Control and Prevention; MSM = men who have sex with men; NAAT = nucleic acid amplification test; NCSP = National Chlamydia Screening Programme; STI = sexually transmitted infection; USPSTF = US Preventive Services Task Force; WSW = women who have sex with women.

Table 3

Treatment Regimens for *C. trachomatis* Infections [35]

	Non-pregnant Women and Men	Pregnant Women
Preferred	**Azithromycin** 1 g orally in single dose OR **Doxycycline** 100 mg orally twice a day for 7 days	**Azithromycin** 1 g orally in a single dose OR **Amoxicillin** 500 mg orally three times a day for 7 days
Alternative	**Erythromycin** base 500 mg orally QID x7 days OR **Erythromycin** ethylsuccinate 800 mg orally four times a day for 7 days OR **Levofloxacin** 500 mg orally once daily for 7 days OR **Ofloxacin** 300 mg orally twice a day for 7 days	**Erythromycin** base 500 mg orally four times a day for 7 days OR **Erythromycin** base 250 mg orally four times a day for 14 days OR **Erythromycin** ethylsuccinate 800 mg orally four times a day for 7 days OR **Erythromycin** ethylsuccinate 400 mg orally four times a day for 14 days

Note: Patients infected with HIV should receive the same treatment regimen as those who are HIV-negative.