CLINICAL PRACTICE

Genital Chlamydial Infections

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

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N Engl J Med 2003;349:2424-30.

A 19-year-old woman visits her primary care provider for counseling about contraception. She became sexually active one year previously and has had a new sexual partner for the past three months. Her partner currently uses a condom intermittently for contraception, and she inquires about oral contraceptives. She reports no medical problems and is in good health. Her physical examination is unremarkable. Is testing for *Chlamydia trachomatis* indicated?

THE CLINICAL PROBLEM

Chlamydia trachomatis is the most common bacterial cause of sexually transmitted infections in the United States, responsible for an estimated 3 million new infections each year.[1,2] The cost of care for untreated chlamydial infections and their complications is estimated to exceed $2 billion annually.[3]

CLINICAL PRESENTATION

As many as 85 to 90 percent of *C. trachomatis* infections in men and women are asymptomatic.[4,5] Asymptomatic infections can persist for several months.[5] Despite the frequent absence of symptoms, at least one third of women have local signs of infection on examination.[5] The two most commonly reported signs are mucopurulent discharge from the cervix and hypertrophic cervical ectopy (Fig. 1). Signs and symptoms in men include urethral discharge of mucopurulent or purulent material, dysuria, or urethral pruritus.

Clinical manifestations of *C. trachomatis* infections in women include acute urethral syndrome, urethritis, bartholinitis, cervicitis, upper genital tract infection (endometritis, salpingo-oophoritis, or pelvic inflammatory disease), perihepatitis (Fitz-Hugh–Curtis syndrome), and reactive arthritis.[5] Symptoms depend on the site of infection. Infection of the urethra and lower genital tract may cause dysuria, abnormal vaginal discharge, or postcoital bleeding, whereas infection of the upper genital tract (e.g., endometritis or salpingitis) may be manifested as irregular uterine bleeding and abdominal or pelvic discomfort.

In women, untreated chlamydial infection can lead to severe reproductive complications. *C. trachomatis* is an important causal agent in pelvic inflammatory disease, with sequelae including infertility, ectopic pregnancy, and chronic pelvic pain.[6] Up to two thirds of cases of tubal-factor infertility and one third of cases of ectopic pregnancy may be attributable to *C. trachomatis* infection.[7] Chlamydial infection during pregnancy is associated with a number of adverse outcomes of pregnancy including preterm labor, premature rupture of the membranes, low birth weight, neonatal death, and postpartum endometritis.[8,9]

Chlamydial infection during pregnancy may be transmitted to the infant during de-

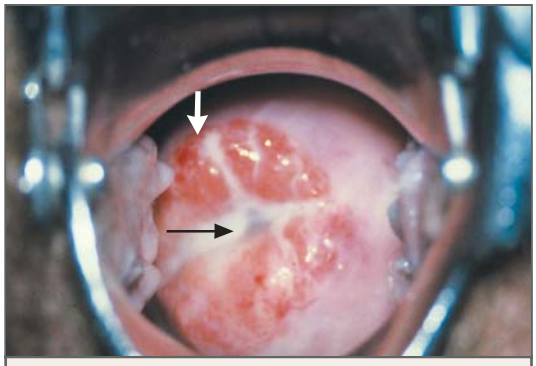

Figure 1. Cervical Ectropion (White Arrow) with Mucopurulent Cervicitis (Black Arrow).
Photograph courtesy of Dr. Marc Steben.

livery.[10] An infant born to a mother with active infection has a risk of acquiring infection at any anatomical site of 50 to 75 percent. Approximately 30 to 50 percent of infants born to chlamydia-positive mothers will have conjunctivitis, and at least 50 percent of infants with chlamydial conjunctivitis will also have nasopharyngeal infection. Chlamydial pneumonia develops in about 30 percent of infants with nasopharyngeal infection.[5]

In men, the most common clinical manifestation of *C. trachomatis* infection is nongonococcal urethritis. In fact, *C. trachomatis* causes approximately 35 to 50 percent of all cases of nongonococcal urethritis in heterosexual men. Symptoms of nongonococcal urethritis may develop after an incubation period of 7 to 21 days and include dysuria and mild-to-moderate whitish or clear urethral discharge. In most cases, physical examination reveals no abnormalities other than the discharge. Other clinical syndromes in men include acute epididymitis, acute proctitis, acute proctocolitis, conjunctivitis, and Reiter's syndrome.[5] Male infertility, chronic prostatitis, and urethral strictures are possible results of infection. Both Reiter's syndrome (urethritis, conjunctivitis, arthritis, and mucocutaneous lesions) and reactive tenosynovitis or arthritis (without the other components of Reiter's syndrome) have been associated with genital *C. trachomatis* infection.[5] Infection with *C. trachomatis* is also believed to be a cofactor for the transmission of human immunodeficiency virus in both men and women.[11]

EPIDEMIOLOGY OF CHLAMYDIAL INFECTIONS

The prevalence of chlamydia depends on the characteristics of the population studied. Reported prevalence rates in the United States have ranged from 2 to 7 percent among female college students and 4 to 12 percent among women attending a family planning clinic to 6 to 20 percent among men and women attending a clinic for sexually transmitted diseases or persons entering correctional facilities.[5,12] In the United Kingdom, recent data suggest that the rate of infection among young women exceeds 10 percent.[13] The prevalence of *C. trachomatis* infection is highest in groups of persons who are the least likely to see a clinician. Prevalence rates have declined in geographic areas where screening programs have been implemented.[14]

Risk factors for chlamydial infection in sexually active women include a young age (less than 25 years and, in particular, less than 20 years), intercourse at an early age, having more than one sexual partner, involvement with a new sexual partner, being unmarried, black race, a history of or coexistent sexually transmitted infection, cervical ectopy, and inconsistent use of barrier contraceptive methods.[15,16] Young age is the factor that is most strongly associated with infection (relative risk among women younger than 25 years as compared with older women, 2.0 to 3.5).[17] This association is largely attributable to the higher level of sexual activity among younger women. Also, in younger women, the squamocolumnar junction of the cervix often lies well out on the ectocervix, forming a bright red central zone of ectopic columnar epithelium called an ectropion (Fig. 1); this ectopy provides a larger target area for chlamydial infection than is present in older women.[18]

STRATEGIES AND EVIDENCE

SCREENING

Screening in Women

There is good evidence that screening women who are at risk for *C. trachomatis* infection can prevent reproductive sequelae by reducing the rate of pelvic inflammatory disease.[15] The strongest evidence supporting screening in women comes from a large randomized trial of screening and treatment at a health maintenance organization in Seattle.[19] Participants were unmarried, asymptomatic women (18 to 34 years of age) who were considered to have a high risk of *C. trachomatis* infection on the basis of a scoring system that included as risk factors a young age (less than 25 years), black race, nulligravidity, douching, and two or more sexual partners during the previous 12 months. By the end of the

follow-up period, there were 9 verified cases of pelvic inflammatory disease in the screened group (8 per 10,000 woman-months of follow-up) and 33 cases in the usual-care group (18 per 10,000 woman-months; relative risk in the screened group, 0.44; 95 percent confidence interval, 0.20 to 0.90). Long-term adverse outcomes of chlamydial infection were not addressed in this study.

In addition, two ecologic studies (studies evaluating associations between types of exposure and outcomes in populations rather than individual persons), conducted in Sweden, showed that the rates of both ectopic pregnancies and pelvic inflammatory disease were reduced in communities after screening for chlamydial infection was adopted.[20,21] However, it is possible that the lower prevalence of adverse outcomes in these studies was due to factors other than screening, such as increased use of barrier contraceptives and reductions in risk-taking behavior.

Although data from randomized trials of screening for chlamydial infection during pregnancy are lacking, there is some evidence that screening high-risk women for *C. trachomatis* during pregnancy can reduce the rate of adverse outcomes of pregnancy. Two observational studies showed associations between the treatment of chlamydial infections during pregnancy and improved outcomes of pregnancy, including lower rates of premature rupture of the membranes, low birth weight, births of infants who were small for their gestational age, and neonatal death.[22,23]

Screening in Men

The U.S. Preventive Services Task Force found no direct evidence to determine whether screening asymptomatic men is effective for reducing the incidence of new infections in women, and it could not determine the balance of the harms and benefits of screening men.[15]

Testing Methods

The gold standard for the diagnosis of *C. trachomatis* infection was traditionally a culture of a swab from the endocervix in women or the urethra in men. However, the methodologic challenges of culturing this organism led to the development of non–culture-based tests. Whereas early non–culture-based tests, including antigen-detection tests and nonamplified nucleic acid hybridization, were limited by their failure to detect a substantial proportion of infections,[24] newer tests that amplify and detect *C. trachomatis*–specific DNA or RNA sequences[25] (including polymerase chain reaction, ligase chain reaction, and transcription-mediated amplification of RNA) are substantially more sensitive than the first-generation non–culture-based tests (80 to 91 percent, depending on the site from which the specimen is obtained, vs. 62 to 75 percent), when culture is used as the gold standard.[25] The sensitivity is slightly lower when these newer tests are performed on urine specimens rather than endocervical specimens, but the specificity is high for all types of specimens (range, 94 to nearly 100 percent).[25] The majority of nucleic acid–amplification tests have been approved by the Food and Drug Administration for the detection of *C. trachomatis* (and *Neisseria gonorrhoeae*) in urine from both men and women, providing a noninvasive testing method.[25] Limitations of nucleic acid–amplification tests include their relatively high cost and the requirement for a suitable laboratory.[25]

The most recent addition to the testing armamentarium is the use of specimens collected by patients.[26,27] Amplification testing of vaginal or urethral swab specimens collected by patients has a sensitivity and specificity similar to those of amplification testing of specimens collected by clinicians, and studies indicate that patients prefer this method to the standard collection methods.[28,29]

TREATMENT

The treatment of chlamydial infection depends on the clinical syndrome (Table 1).[2] Effective and low-cost treatments for genital chlamydial infection are available for the most common clinical syndromes (nongonococcal urethritis in men and mucopurulent cervicitis in women). In a randomized trial, the efficacy of a seven-day course of doxycycline was equivalent to that of a single dose of azithromycin; both resulted in cure rates of more than 95 percent among men and nonpregnant women.[30] Sexual partners should be notified, examined, and treated for chlamydia and any other identified or suspected sexually transmitted disease. Patients and their partners should be instructed to refrain from sexual intercourse until therapy is completed (specifically, until seven days after a single-dose regimen or until the completion of a seven-day regimen).[2]

Infection during Pregnancy

A Cochrane review of 11 randomized trials for the treatment of chlamydia during pregnancy concluded that amoxicillin was as effective as oral erythro-

Table 1. Common Clinical Syndromes and Their Treatment.

Syndrome	Recommended Regimens
Men	
Nongonococcal urethritis	Azithromycin, 1 g orally (single dose), or doxycycline, 100 mg orally 2 times a day for 7 days
Recurrent or persistent urethritis	Metronidazole, 2 g orally (single dose), plus erythromycin base, 500 mg orally 4 times a day for 7 days, or erythromycin ethylsuccinate, 800 mg orally 4 times a day for 7 days
Epididymitis	Ceftriaxone, 250 mg intramuscularly (single dose), plus doxycycline, 100 mg orally 2 times a day for 10 days
Women	
Mucopurulent cervicitis	Azithromycin, 1 g orally (single dose), or doxycycline, 100 mg orally 2 times a day for 7 days
Chlamydia during pregnancy	Erythromycin base, 500 mg orally 4 times a day for 7 days, or amoxicillin, 500 mg orally 3 times a day for 7 days, or azithromycin, 1 g orally (single dose)
Pelvic inflammatory disease	
Outpatient	Ofloxacin, 400 mg orally 2 times a day for 14 days, or levofloxacin, 500 mg orally once a day for 14 days, with or without metronidazole, 500 mg orally 2 times a day for 14 days; otherwise, ceftriaxone, 250 mg intramuscularly (single dose), or cefoxitin, 2 g intramuscularly (single dose), plus probenecid, 1 g orally, plus doxycycline, 100 mg orally 2 times a day for 14 days, with or without metronidazole, 500 mg orally 2 times a day for 14 days
Inpatient*	Cefotetan, 2 g intravenously every 12 hours, or cefoxitin, 2 g intravenously every 6 hours, plus doxycycline, 100 mg orally or intravenously every 12 hours; otherwise, clindamycin, 900 mg intravenously every 8 hours, plus gentamicin, 2 mg per kg of body weight loading dose intravenously, then 1.5 mg per kg every 8 hours; daily administration of a single dose may be substituted

* Therapy for pelvic inflammatory disease should be continued for 24 to 48 hours after clinical improvement occurs and should consist of continuous oral therapy with doxycycline, 100 mg orally twice a day, or clindamycin, 450 mg orally 4 times a day, for a total of 14 days.

mycin.[31] Several small trials comparing oral azithromycin with these therapies have shown similar cure rates and acceptability for azithromycin.[32,33]

Pelvic Inflammatory Disease

Although pelvic inflammatory disease is thought to be a polymicrobial infection, *C. trachomatis* is one of the more common pathogens involved. The minimal criteria for a diagnosis of pelvic inflammatory disease include uterine–adnexal tenderness or cervical-motion tenderness.[2] Some studies suggest that atypical presentations of pelvic inflammatory disease, including discomfort without appreciable tenderness, abnormal uterine bleeding, and abnormal vaginal discharge, are often associated with infection and inflammation in the upper genital tract (i.e., endometritis and salpingitis).[34,35] Chlamydial pelvic inflammatory disease tends to have a more insidious onset than pelvic inflammatory disease caused by *N. gonorrhoeae* or other more virulent organisms. However, the damage to the fallopian tube can be as great or greater with chlamydia, especially with repeated infections.[36]

Because of the risks of infertility and other sequelae of pelvic inflammatory disease, clinicians should have a low threshold for the prompt institution of treatment in women who are at risk for chlamydial infection. The delay of antibiotic therapy is associated with an increased risk of adverse outcomes.[37] The PID [Pelvic Inflammatory Disease] Evaluation and Clinical Health (PEACH) study, a randomized trial comparing inpatient therapy consisting of cefoxitin and doxycycline with similar outpatient therapy, demonstrated that outpatient therapy for uncomplicated pelvic inflammatory disease (without tubo-ovarian abscess or severe illness) was as effective as intravenous inpatient therapy in terms of fertility and other long-term health outcomes, including the prevention of ectopic pregnancy and chronic pelvic pain.[38]

AREAS OF UNCERTAINTY

There continues to be uncertainty regarding whom to screen and how frequently to do so. There is little evidence of the effectiveness of screening in asymptomatic women who are not in high-risk groups.[15] Screening on the basis of age (less than 25 years) appears to be effective even in areas where the prevalence of chlamydial infection is low to moderate

(3 to 6 percent). In a longitudinal cohort study of screening in 3202 high-risk, inner-city young women, chlamydial infection was detected in 24.1 percent; the median time to new infection was slightly more than 7 months, and the median time to a repeated positive test was 6.3 months. On the basis of these results, it was recommended that all young, sexually active women be screened every six months.[39] It is unclear, however, whether these findings can be generalized to populations with a lower prevalence of infection.

Level I evidence (from randomized trials) is also lacking regarding the effectiveness of the screening and treatment of pregnant women in populations with a low prevalence of chlamydial infection. In addition, the balance of benefits and harms (including false-positive test results and the inappropriate use of antibiotics) has not been assessed.[15]

Given the high prevalence of asymptomatic infections in the population, some experts advocate for the routine screening of young men as the next important step toward reduced rates of infections and complications.[40,41] Although there is strong evidence that treatment can eradicate *C. trachomatis* infection in men, there are no studies demonstrating that the screening of asymptomatic men can reduce the rates of acute infection and adverse outcomes in men or in women. Cost-effectiveness analyses have suggested that there is an economic benefit to society of screening for *C. trachomatis*, as compared with not screening, in high-risk women.[42,43] However, the cost effectiveness of the screening of men and low-risk women is debatable and will depend on the prevalence of infections, the ease and cost of specimen collection, the cost of testing, the characteristics of the diagnostic tests (e.g., their sensitivity and specificity), and the short- and long-term adverse outcomes that are prevented. Additional research is needed to determine the optimal interval between screenings and to compare the universal screening of all sexually active women younger than 25 years of age with screening based on the presence of additional risk factors in populations with a range of prevalence rates.

It remains uncertain whether the routine use of urine specimens or specimens collected by patients would improve compliance with testing and treatment. Also, it is unclear whether the empirical treatment of the sexual partners of patients with chlamydial infections is preferable to the screening of these partners. Some experts suggest that providing patients with prescriptions for empirical treatment to deliver to their sexual partners will reduce the rate of reinfection,[44] but this hypothesis remains unproven. In a recent trial in which patients were randomly assigned to either patient-delivered treatment for partners (patients were asked to deliver a dose of azithromycin to each of their sexual partners) or self-referral (patients were asked to refer their sexual partners for treatment), the risk of reinfection was nonsignificantly lower in the group assigned to patient-delivered treatment (odds ratio for reinfection, 0.8; 95 percent confidence interval, 0.6 to 1.1).[45]

GUIDELINES

Guidelines from several professional societies, the Centers for Disease Control and Prevention, and the U.S. Preventive Services Task Force are summarized in Table 2.[46-50] All groups suggest that clinicians screen routinely for *C. trachomatis* in all sexually active women less than 25 years of age and in other asymptomatic women who are at increased risk for infection.

CONCLUSIONS AND RECOMMENDATIONS

Screening for *C. trachomatis* infection is indicated in sexually active women with risk factors for this infection, including an age of less than 25 years, inconsistent use of barrier contraceptives, a new sexual partner, more than one sexual partner, cervical ectopy, and a history of or coexisting sexually transmitted disease. The patient described in the vignette has some of these risk factors. Electing not to screen her would place her at risk for adverse outcomes, including ascending infection (pelvic inflammatory disease) and infertility, chronic pelvic pain, and ectopic pregnancy. Annual screening is reasonable, although more frequent testing may be indicated in areas of high prevalence or in women with several risk factors. Information on prevalence (the rates of positive tests) can often be obtained from microbiology laboratories. The use of barrier contraception (e.g., condoms) as a method of prevention should be discussed with all patients. If a screening test is positive for *C. trachomatis*, I would treat the patient with doxycycline or azithromycin. Retesting (a "test of cure") after treatment with recommended regimens is not indicated unless compliance is in question, symptoms are present, or reinfection is suspected.[2] Rescreening for chlamydia is recom-

Table 2. Guidelines from Professional Societies and Federal Agencies.

Organization	Who Should Be Screened	Timing or Frequency of Screening
American Academy of Pediatrics[46]	All young, sexually active women	Perform annually
American College of Obstetricians and Gynecologists[47]	All young sexually active women and other women at high risk for infection	Perform routinely (interval not specified)
American College of Preventive Medicine[48]	All sexually active women with risk factors (age ≤25 yr, new male sexual partner or two or more sexual partners in previous year, inconsistent use of barrier contraceptives, history of sexually transmitted disease, black race, cervical ectopy)	Perform annually
	Pregnant women	Perform during first trimester in all women, third trimester if risk factors present
American Medical Association[49]	All young, sexually active women	Perform annually
Canadian Task Force on Preventive Health Care[50]	Persons in high-risk groups (sexually active women <25 yr of age, men and women with a new sexual partner or more than one partner in the previous year, women who use nonbarrier contraceptive methods)	Not specified
	Pregnant women	Perform during first trimester in all women
Centers for Disease Control and Prevention[2]*	All sexually active women <20 yr of age; women 20–24 yr of age if one of the following risk factors is present: inconsistent use of barrier contraceptives or a new sexual partner or multiple sexual partners during the previous 3 mo; women >24 yr of age if both risk factors are present	Perform annually
	Pregnant women	Perform during first prenatal visit in all women, third trimester if high risk (<25 yr of age or other risk factors)
U.S. Preventive Services Task Force[15]†	All sexually active women ≤25 yr of age and other asymptomatic women at increased risk for infection	Perform routinely, optimal interval uncertain
	All asymptomatic pregnant women ≤25 yr of age and others at increased risk for infection	Perform routinely, optimal interval uncertain

* The guidelines of the Centers for Disease Control and Prevention are available at http://www.cdc.gov/std/treatment/rr5106.pdf.
† The guidelines of the U.S. Preventive Services Task Force are available at http://www.ahrq.gov/clinic/uspstf/uspschlm.htm. The task force recommends routine screening in the groups listed and notes that there is insufficient evidence to make a recommendation for or against screening in asymptomatic men.

mended when patients present for care within 12 months after a positive test.[2]

The timely treatment of the patient's sexual partners is also essential in order to reduce the risk of reinfection. The sexual partners should be evaluated, tested, and treated if they have had sexual contact with the patient during the 60 days preceding the diagnosis. Treatment for sexual partners that is delivered by the patient for the prevention of repeated infection has efficacy similar to that of self-referral and is a reasonable approach.

Supported in part by a Midcareer Investigator Award in Women's Health Research from the National Institute of Child Health and Human Development (K24 HD01298-03).

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