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Chlamydial Infections

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INTRODUCTION

Chlamydia trachomatis is the most commonly reported infectious disease in the United States and is the most common sexually transmitted bacterial infection (1). The word *chlamys* is Greek for “cloaked” or “draped,” descriptive of the intracytoplasmic inclusion bodies that are “draped” around the host cell nucleus. A large reservoir of infection sustains the continued spread of *C. trachomatis* because chlamydial infections rarely cause symptoms in women, they have a long incubation period, and the infection persists for at least several months. The annual cost of short- and long-term impacts of chlamydial infections in the United States was estimated to be \$2.4 billion in 1987 and has increased since that time (2).

FAST FACTS

- Chlamydia is the most commonly reported bacterial infection, with an estimated 2.8 million new cases each year.
- Adolescents and young adults are most commonly infected with *C. trachomatis*.
- By age 30, 50% of US women carry antibodies, indicating prior exposure.
- The majority of infections with *C. trachomatis* in both men and women are asymptomatic.
- Up to 40% of untreated chlamydial cervicitis cases will ascend into the upper genital tract, where considerable tubal damage can occur with very few symptoms.
- All sexually active women under age 26 should be screened at least annually. Such screening has been demonstrated to reduce the incidence of upper tract infection.
- Mucopurulent cervicitis is treated with the same therapy as chlamydial cervicitis.

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PREVALENCE AND INCIDENCE

In 2000, the Centers for Disease Control and Prevention (CDC) required states to report all cases of chlamydia. Even with this requirement in place, it is believed that chlamydial infections are significantly underreported because of sporadic screening and the use of outdated (insensitive) tests. Local studies demonstrated that the prevalence of infected and untreated cases equals or exceeds the number of cases that were diagnosed and treated (3). The CDC estimates that 2.8 million new cases occur in the United States each year (4). Nearly 75% of cases occur in the 15- to 24-year-old age group (5). The World Health Organization estimated that 92 million new infections with *C. trachomatis* occurred worldwide in 1999 (6).

Women primarily are most likely to be diagnosed with infection and to suffer more severe, long-term consequences. Chlamydia infection rates were 3.3 times higher in women than men in 2004 in the United States. Of the 929,462 cases reported to the CDC in 2004, 78% were women (4). Antibody testing demonstrates that nearly 50% of women have been exposed to *C. trachomatis* by age 30 (7). The prevalence of active infection in sexually active, asymptomatic, non-pregnant women in the general population is between 3 and 5% (8). The highest age-specific rates were reported in women age 15–26. Among men, the highest rate occurs in 20- to 24-year-olds (1). The National Longitudinal Study of Adolescent Health tested the urine of more than 12,000 young adults ages 18–26 and found the overall prevalence of chlamydial infection was 4.19%, and ranged from 1.94 to 12.54%, depending on demographics (9). Women in family planning clinics have a background rate of 2.8–9.4%, whereas patients in sexually transmitted disease (STD) clinics are found to have a 15–33% incidence (8). About 9% of female military recruits (10), 10.3% of Job Corps women (11), 9.9–27% of teen women in juvenile detention centers (11a,12), and 6% of women seeking elective abortions have acute chlamydial infections (13).

In the general population, men have the same prevalence of chlamydial infections as women (3–5%). In STD clinics, the prevalence rates among men are 15–20%, which is slightly less than the rates among women (8). Chlamydial infections are found in 13–15% of sexually active men in adolescent clinics. The prevalence of chlamydial infection in men who have sex with men (MSM) varies by anatomical site: rectal 7.9%, urethral 5.2%, and pharyngeal 1.4% (14).

Chlamydia is often found as a co-infection with gonorrhea in both men and women. Between 30 and 50% of patients who have gonococcal infections also have infection with *C. trachomatis*. However, because the background incidence of gonorrhea is so much lower (<0.5%), it is far less likely that a person infected with *C. trachomatis* will also have gonococcal infection. In the National Longitudinal Study, only 0.3% of young adults were co-infected (9).

RISK FACTORS

Specific historical and behavioral factors place a patient at an increased risk for acquisition of *C. trachomatis*. The classic risk factors for chlamydial infection include age younger than 26, low socioeconomic status, minority group member, multiple sexual partners, and new partners. Age is an important risk factor because *C. trachomatis* typically infects the columnar cells of the cervix; in younger women, columnar cells are more likely to be on the ectocervix (ectopy), where they can be exposed to semen carrying the organism. As women age, the columnar cells are located higher in the cervical canal. Combination hormonal contraceptive use apparently increases cervical ectopy and has been a proposed risk factor chlamydial infection (15). African-American women are disproportionately impacted by chlamydia. In 2004, the rate of chlamydia infection among black women was 7.5 times higher than in white women (1).

INFECTIVITY AND TRANSMISSION

C. trachomatis is a relatively infectious agent. More than two-thirds of female partners of men with culture-positive chlamydial urethritis have chlamydial infection themselves (8). The single exposure male-to-female transmission rate has been estimated to be 40%, and the female-to-male transmission rate has been estimated to be 32% (8). Other investigators have found that transmission rates between sexes are equivalent (16). Vertical transmission of *C. trachomatis* is more efficient than horizontal transmission. More than 60% of newborns who deliver through a chlamydia-infected cervix will acquire the infection (8).

ETIOLOGY

C. trachomatis is one of four species of the genus *Chlamydia*. It is responsible for a wide range of infections, including trachoma (a chronic conjunctivitis, which is the leading preventable cause of blindness worldwide), newborn conjunctivitis, and genital infections in women and men. *C. trachomatis* is an obligate intracellular organism, dependent on the host cell's adenosine triphosphate (ATP) production. *C. trachomatis* has a unique life cycle, which differentiates it from all other microorganisms (see Fig. 1). Infection begins when elemental bodies (EBs) attach to specific receptors found on nonciliated columnar or cuboidal epithelium of the host. This type of epithelium is located in the endocervix, endometrium, fallopian tube, and urethra, making those sites vulnerable to infection.

The host cell ingests the organism by a chlamydia-specific phagocytic process. After phagocytosis, the EB exists within a cytoplasmic vacuole or phagosome, where it is protected from host defense systems. Within the phagosome, the EB transforms into a reticulate body (RB) in order to multiply. It multiplies

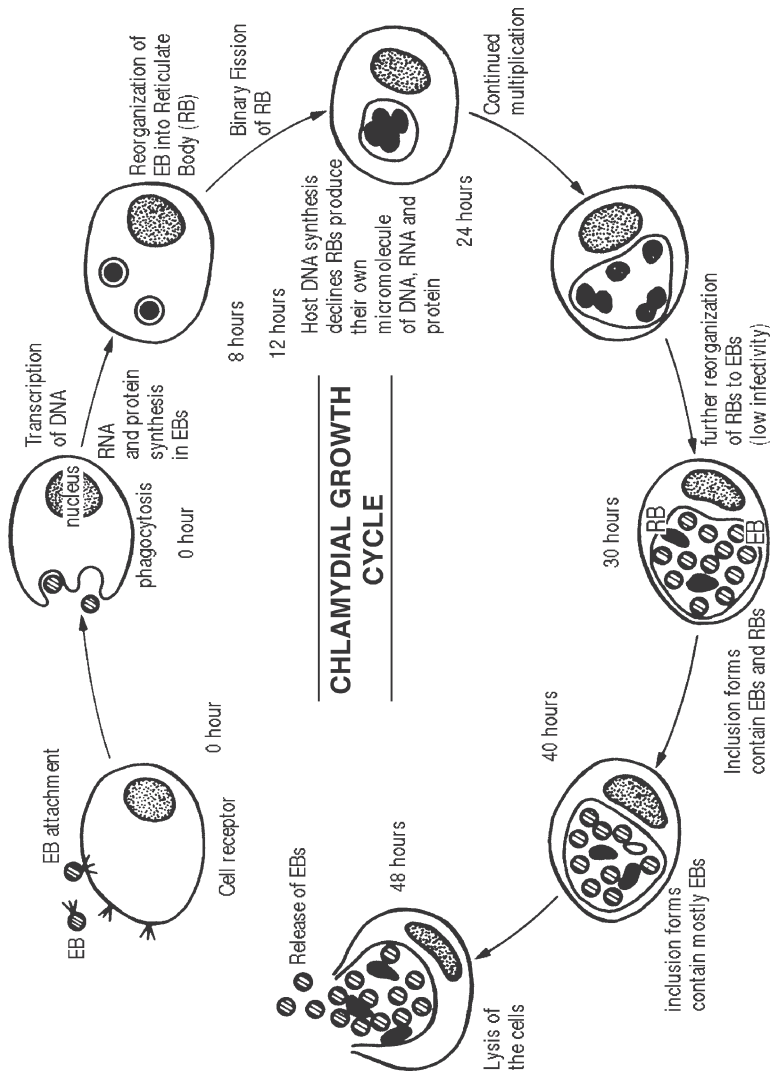


Fig. 1. Chlamydial growth cycle.

by binary fusion after duplicating its own DNA, RNA, and proteins by using host ATP. The RBs then reorganize back into EBs, the infectious form of the organism. Ultimately, the host cell undergoes either lysis or exocytosis with release of the EBs, which infect adjacent cells and restart the cycle. This process takes 2–3 days.

C. trachomatis has features of both bacteria and virus. *C. trachomatis* has a cell wall like Gram-negative bacteria but it cannot synthesize its own ATP or grow on artificial media, hence its similarity with a virus. Because of its unique developmental cycle, it is taxonomically classified in a separate order. The chemical composition of the cell wall of the EB is quite similar to that of Gram-negative bacteria. The cell wall of the RB contains less phospholipid than the EB; thus, RBs are highly labile and do not survive outside of the host cell. However, the EB is relatively stable in extracellular environments because its envelope is strengthened owing to cysteine proteins that are cross-linked by disulfide bonds, providing the EB structural integrity and resistance.

C. trachomatis is currently classified into 15 serotypes (serovars): A, B, Ba (AP-2), C, D, E, F, G, H, I, J, K, L1, L2, and L3. Classification is based on the major outer membrane protein using polyclonal and monoclonal antibodies. Typically, different serovars are associated with specific clinical diseases. The ocular disease trachoma is associated with serovars A, B, Ba, and C. Genital disease (exclusive of lymphogranuloma venereum), neonatal conjunctivitis, and pneumonia are associated with serovars of D through K. Serovars L1, L2, and L3 are associated with lymphogranuloma venereum. The different serovars of *C. trachomatis* within groups have not been shown to have different clinical courses (17).

CLINICAL MANIFESTATIONS

The range of infections with *C. trachomatis* is impressive (see Table 1). The predominant infections are urethritis, cervicitis, and proctitis, but chlamydial infection can spread locally to the Bartholin glands, endosalpinges, or epididymis. In pregnancy, chlamydial infection is a risk factor for low-birth weight infants and preterm delivery. Postpartum, an infected woman is at increased risk for developing endometritis. Her newborn can develop conjunctivitis and pneumonia. Men who have chlamydial urethritis are at risk for developing Reiter's syndrome. Each of these clinical infections has a wide spectrum of initial presenting symptoms, ranging from no symptoms to noticeable discomfort and pain.

Infections in Women

CERVICITIS

The cervix is the most common site of infection for women. Women with chlamydial cervicitis generally are asymptomatic or report only nonspecific symptoms, such as vaginal discharge or postcoital spotting or bleeding. Two-

Table 1
Clinical Manifestations of *C. Trachomatis* Infection

| <i>Demonstrated</i> | <i>Suggested</i> | |
|---|---|--|
| Women | | |
| <ul style="list-style-type: none"> • Cervicitis • Urethritis • Acute urethral syndrome • Proctitis • Endometritis • Salpingitis | <ul style="list-style-type: none"> • Perihepatitis • Conjunctivitis • Ectopic pregnancy • Infertility • Chronic pelvic pain • Reiter's syndrome | <ul style="list-style-type: none"> • Preterm labor • Preterm delivery • Premature rupture of membranes • Postpartum endometritis |
| Men | | |
| <ul style="list-style-type: none"> • Urethritis • Ependymitis • Prostatitis • Reiter's syndrome | <ul style="list-style-type: none"> • Proctitis • Infertility • Conjunctivitis | |
| Newborns | | |
| <ul style="list-style-type: none"> • Conjunctivitis • Otitis media | <ul style="list-style-type: none"> • Pneumonia | |

thirds of infected women have no signs or symptoms. Furthermore, because the incubation period for *C. trachomatis* is 6–14 days, women may not relate their subtle symptoms to a distant exposure. Secondary or related infections (trichomoniasis or gonorrhea) are generally the etiology for complaints in women with symptoms.

On speculum exam, the chlamydia-infected cervix may appear entirely normal or may have a mucopurulent discharge and eroded friable appearance. *C. trachomatis* infects only columnar cells in the cervical squamocolumnar region or in the endocervix. In women with cervical ectopy and mucopurulent cervical discharge, *C. trachomatis* should be considered. The presence of leukocytes in endocervical samples studied under magnification is a better predictor of chlamydial infection, when other causes have been ruled out. Testing with sensitive laboratory-based tests (*see* the section on “Testing Techniques”) is needed to confirm the diagnosis and distinguish it from mucopurulent cervicitis.

Bimanual exam should always be performed after appropriate specimens have been collected. Gentle exam for cervical motion tenderness should be performed to assess possible upper tract involvement (*see* the section on “Salpingitis”). Once chlamydial infection is suspected, concrete questions should be asked about sexual practices to identify other sites that might be involved.

URETHRITIS/URETHRAL SYNDROME

Women with chlamydial urethritis are generally asymptomatic. Those who have acute infections may complain of dysuria, slight discharge in urine, or urinary frequency. A woman with chlamydial urethritis/urethral syndrome will note that her symptoms are focused in the suprapubic area and start after she has finished voiding, which may help distinguish that infection from bacterial cystitis. Conventional urinalysis and culture testing will reveal sterile pyuria. Because only selective antibiotics will treat chlamydial infections, the symptoms will not resolve with typical antibiotic therapies for bacterial cystitis. The differential diagnosis includes infection with mycoplasma or ureaplasma, as well as urethral trauma and atrophic urethritis. Direct testing for *C. trachomatis* can be done on specimens obtained by urethral swabs or on urine from the first part of the stream. It is rare for chlamydial urethritis to exist independent of a cervical infection in a woman.

BARTHOLINITIS

The Bartholin's gland and ducts are lined with columnar epithelium and are susceptible to infection with *C. trachomatis*. It has been estimated that 30% of Bartholin infections are abscesses initiated by chlamydial infection, although the absolute contribution is not known (18,19). Women with Bartholin's abscesses complain of acute onset of vulvar pain and swelling, which becomes quite intense as the abscess expands. The symptoms, rapid course of infection, and recommended treatments for chlamydial Bartholin's abscesses are similar to that with gonococcal abscesses (see Chapter 8).

SALPINGITIS

Ascending infection from the lower genital tract occurs in approximately 10% of patients with cervicitis. Sperm has been implicated in the transport of *C. trachomatis* into the upper genital tract in women. Symptoms may appear at any time during a woman's menstrual cycle, in contrast to gonococcal pelvic inflammatory disease (PID), which classically develops at the end of a woman's menses. The clinical presentation of chlamydial salpingitis is much more subtle than gonococcal salpingitis, because the fallopian tubes may not be distended with chlamydial infection even though the endosalpinges may suffer profound architectural damage because of chlamydial heat-shock proteins. Women with significant upper tract infection may be asymptomatic or have only mild flu-like discomforts that they attribute to other causes. Because of this very unremarkable clinical symptomatology and the relative paucity of clinical findings on examination and laboratory testing, the CDC revised its requirements for the criteria of pelvic inflammatory disease to lower the threshold for diagnosis. See Chapter 8 for more information about diagnosis and treatment.

Infections in Men

CHLAMYDIAL URETHRITIS

Nongonococcal urethritis is most commonly caused by *C. trachomatis*. The typical incubation period from exposure to infection is 1–2 weeks. Symptomatic men generally present with complaints of dysuria, urinary frequency, and urethral discharge. The discharge is greatest in the morning when it can be milked from the urethra. A diagnosis of nongonococcal urethritis is made when (1) a Gram-stain of the discharge demonstrates five or more white blood cells per field on high power ($\times 1000$) and there are no diplococci or (2) first voided urine has positive leukocyte esterase and microscopic examination reveals 10 or more white blood cells per high power field (20,21). Urethritis is often asymptomatic; therefore, infected men are a major reservoir for infection of their sexual partners (16).

PROSTATITIS

The symptoms associated with prostatitis are perineal pain, back pain, and pain with urination or ejaculation. Acute prostatitis in young men can occur with *C. trachomatis*. The role of *C. trachomatis* in chronic prostatitis is not as clear. More than one-fourth of men with nonbacterial chronic prostatitis were found to have chlamydial antigens and 80% showed cures after treatment with doxycycline (22). More than one in five men with chronic prostatitis with inflammation seen on prostatic secretions had evidence of chlamydial infection (23). These results suggest that *C. trachomatis* may be one of the causative agents of chronic prostatitis (23).

EPIDIDYMITIS

Tenderness with swelling in the testicle is a sign of epididymitis. Acute epididymitis more commonly occurs in younger men. Other infectious etiologies for epididymitis include *Neisseria gonorrhoea* and *Escherichia coli*. Chlamydial epididymitis has a milder course than other etiologies. Chronic epididymitis is defined as testicular pain persisting for at least 3 months. Because of the indolent nature of chlamydial infections, a patient with chronic epididymitis can also have a scrotal mass. Male infertility may be associated with chlamydial infections because the inflammatory process may damage the epididymis and the tubules. Men with fertility problems have been found by serology to have more likely had a previous infection of Chlamydia, but definitive proof is not yet been established (24).

Infections in Men or Women

PROCTITIS

Chlamydial proctitis can occur in women and MSM who practice receptive anal intercourse. *C. trachomatis* was found in specimens from 5% of rectums and 13% of cervixes of 115 consecutive women presenting for examination. Rectal

bleeding and microscopic evidence of proctitis without diarrhea was commonly found (25). MSM are likely get infected from unprotected anal intercourse. Chlamydial proctitis has been found in 15% of asymptomatic MSM (26). With symptomatic men and women, sigmoidoscopy and appropriate testing for infectious organisms is required. Human immunodeficiency virus (HIV) antibody status should be established. If the patient is HIV-infected, uncommon pathogens need to be considered. With negative HIV tests, treatment for both gonorrhea and chlamydial infections is appropriate.

REACTIVE ARTHRITIS/REITER'S SYNDROME

Reactive arthritis is an inflammatory synovitis in which no viable organisms can be isolated from the joint and is precipitated by an immunological response to an infectious agent. Reiter's syndrome is composed of a triad of conjunctivitis, urethritis, and arthritis. Often individuals will not manifest all elements of the triad. Men are approximately nine times more likely to develop Reiter's syndrome than women are. Multiple joint involvement is common, usually affecting the knees or feet. Joint symptoms develop 2–4 weeks after urogenital infection, but 10% of affected individuals have no history of urethritis. Conjunctivitis and associated iritis and uveitis usually develop after the arthritis. A scaly skin rash (keratoderma blenorrhagica) on the palms or soles is also seen.

Many organisms have been implicated in reactive arthritis and Reiter's syndrome, including *C. trachomatis*. In genetically susceptible individuals, the immune system reacts to the infectious agent leading to the inflammatory response in the synovial surface (27). Evidence of urogenital *C. trachomatis* was found in 36 to 61% of cases of Reiter's syndrome and chlamydial inclusions may be found in the fibroblast-like synovial cells (28).

Chlamydial Infection in the Newborn

Neonatal chlamydial infection usually develops from vertical transmission. In one study, 6 out of 10 infants who delivered vaginally to mothers with infections had serological evidence of infection. The clinical manifestations varied; 18% of exposed infants developed neonatal conjunctivitis and 16% had pneumonia. Subclinical rectal and vaginal infections also occurred in the newborn (29). Although the most common method of transmission is thought to be direct contact as the fetus delivers through an infected cervix, there have been reported instances where neonatal infection occurred with cesarean section delivery, with and without ruptured membranes (30).

Chlamydial neonatal conjunctivitis has an incubation period of 10–14 days. The orbit of the eye swells and exudates are seen. *C. trachomatis* will be found in a high proportion of specimens. Because *C. trachomatis* can also be found in the nasopharynx, systemic treatment is required rather than a local ophthalmic solution. Twenty percent of untreated neonates will develop neonatal pneumonia

without conjunctivitis (31). Pneumonia occurs between the 4th and 12th week of life, with the majority of newborns becoming symptomatic by the 8th week. They may present with failure to thrive, decreased appetite, and some lethargy. More severely infected infants will present with tachypnea and a staccato-like cough. Upper respiratory symptoms include congestion and nasal passage obstruction without significant nasal discharge. Serious acute complications may require prolonged hospitalization and intubation with ventilator support. Diagnosis can be made by assessing *C. trachomatis* immunoglobulin (Ig)M antibody titers. Long-term complications of pneumonia can include abnormal pulmonary function tests and asthma (32).

TESTING TECHNIQUES

Many tests are available today to detect *C. trachomatis* infection in a wide variety of specimens. Urogenital infections in women can be diagnosed by testing urine or swab specimens from the cervix or vagina. In men, urine tests or swabs of the urethra can be used. Rectal infection can be diagnosed by using rectal swabs. However, there are considerable differences in their respective abilities to detect infection. Selection of the appropriate test, and the need for possible confirmatory tests, depend in large part on the prevalence of the infection in local populations. Therefore, familiarity with the different tests and their properties is needed to enhance detection of infected individuals and to reduce false-positive results. See Table 2 for a summary of the different tests and testing sites by indication.

The most common tests used today are nonculture tests, although tissue culture tests are still required for some applications. Nonculture tests use a variety of techniques that bind tags to specific chlamydia proteins. The most sensitive and accurate of the nonculture tests are the nucleic acid amplification tests (NAATs). NAATs test for a unique nucleic acid (DNA or RNA) of the chlamydial organism or use a probe that is attached to the target nucleic acid. NAATs are very sensitive; they can detect a single gene copy. NAATs are also very specific.

There are several types of NAATs. The two most commonly used tests are the polymerase chain reaction (PCR) and ligase chain reaction (LCR) tests. PCR amplifies the nucleic acids found on the *C. trachomatis* elementary body (EB). PCR has a sensitivity of 90% and a specificity of 99–100%. PCR tests are approved for cervical, male urethral swabs, and male urine specimens. LCR has an overall sensitivity of 94% and a specificity of 99–100%. LCR can be used to test urethral and cervical swabs, as well as first-voided urine. More recently, LCR has been refined for use with liquid cytology specimens to test for *C. trachomatis* and *N. gonorrhoea*. Because NAATs detect DNA and RNA targets, they do not require viable organisms to detect infection. Therefore, if test of cure is needed, it should be delayed until all the chlamydial DNA/RNA has cleared, which usually takes more than 3 weeks.

Table 2
 Recommendations for Test Selection for Common Chlamydial Infections

| <i>Endocervical swabs/urethral swabs</i> | <i>Test selection</i> |
|---|--|
| <i>Indication for testing</i> | |
| <ul style="list-style-type: none"> • Screening <ul style="list-style-type: none"> ◆ Females: when pelvic examination is indicated ◆ Males: urine might be more acceptable to asymptomatic males • Endocervicitis • Urethritis (males) • Diseases at other anatomic locations possibly caused by sexually acquired <i>C. trachomatis</i> infection <ul style="list-style-type: none"> ◆ Pelvic inflammatory disease ◆ Urethral syndrome ◆ Bartholinitis ◆ Epididymitis ◆ Perihepatitis (Fitz-Hugh-Curtis syndrome) (females) ◆ Proctitis ◆ Reactive arthritis/Reiter's syndrome ◆ Conjunctivitis • Not recommended for prepubertal children | <ul style="list-style-type: none"> • Nucleic acid amplification tests (NAATs) <ul style="list-style-type: none"> ◆ Preferred because of high sensitivity relative to other tests • Nonculture/non-NAAT <ul style="list-style-type: none"> ◆ Recommended when a NAAT is not available or not economical • Culture <ul style="list-style-type: none"> ◆ Preferred when an isolate is needed (e.g., sexual abuse or treatment failure) ◆ Point-of-care tests ◆ Recommended only when the patient is likely to be lost to follow-up and when the test will be performed while the patient waits for results and possible treatment • Additional testing is recommended after an initial positive screening test if a low positive predictive value can be expected or if a false-positive result would have serious psychosocial or legal consequences |
| <i>Urethral swabs from women</i> | |
| <i>Indication for testing</i> | <i>Test selection</i> |
| <ul style="list-style-type: none"> • Used with endocervical swab to increase sensitivity of culture for screening • Urethral syndrome | <ul style="list-style-type: none"> • Culture • Nonculture tests are not recommended |

(Continued on next page)

Table 2 (Continued)
 Recommendations for Test Selection for Common Chlamydial Infections

| <i>Urine</i> | <i>Indication for testing</i> | <i>Test selection</i> |
|---|--|-----------------------|
| <ul style="list-style-type: none"> • Females: screening or testing • Males: screening | <ul style="list-style-type: none"> • NAAT <ul style="list-style-type: none"> ◆ Recommended on the basis of increased sensitivity and ease of use ◆ For males, sensitivity with urine has been lower than with urethral swab in the majority of studies, but not all ◆ Other tests are not recommended because of low sensitivity and, in the case of enzyme immunoassay (EIA) and lipopoly-saccharide (LPS)-specific direct fluorescent antibody (DFA) tests, lower specificity ◆ Additional testing is recommended after an initial positive screening test if a low positive predictive value can be expected or if a false-positive result would have serious psychosocial or legal consequences | |
| Rectal swabs | <i>Indication for testing</i> | <i>Test selection</i> |
| <ul style="list-style-type: none"> • Patients with history of receptive anal intercourse • Proctitis • Possible sexual abuse, children | <ul style="list-style-type: none"> • Culture <ul style="list-style-type: none"> ◆ Preferred when an isolate is needed (e.g., sexual abuse) ◆ Sensitivity not well-defined; high specificity, especially if <i>C. trachomatis</i>-specific stain is used ◆ Not readily available in most labs • DFA <ul style="list-style-type: none"> ◆ FDA-cleared for use with rectal specimens ◆ Limited evaluation in published studies ◆ Sensitivity not well-defined; potentially high specificity if <i>C. trachomatis</i>-specific stain is used • Other tests are not recommended <ul style="list-style-type: none"> ◆ NAAT <ul style="list-style-type: none"> ▪ Although crossreactivity with other rectal bacteria has not been reported for NAATs, they have received only limited evaluation in published studies ▪ Some non-commercial labs have initiated NAAT tests that meet CLIA standards | |

Pharyngeal swabs

Indication for testing

- Patients concerned regarding exposure during fellatio or cunnilingus
- Newborns or infants (nasopharyngeal specimens)
 - ◆ Neonatal conjunctivitis
 - ◆ Pneumonia consistent with *C. trachomatis* etiology
- Possible sexual abuse, children

Test selection

- Culture
 - ◆ Preferred method
 - ◆ Necessary when an isolate is needed (e.g., sexual abuse)
 - ◆ Sensitivity not well-defined; high specificity, including if *C. trachomatis*-specific stain is used
- DFA
 - ◆ FDA-cleared for use with pharyngeal specimens
 - ◆ Limited evaluation in published studies
 - ◆ Sensitivity not well-defined; potentially high specificity if *C. trachomatis*-specific stain is used
- Other tests are not recommended
 - ◆ NAAT
 - Although crossreactivity with other pharyngeal bacteria has not been reported for NAATs, they have received only limited evaluation in published studies

Conjunctivae swabs

Indication for testing

- Conjunctivitis among adults
- Newborns or infants
 - ◆ Neonatal conjunctivitis
 - ◆ Pneumonia consistent with *C. trachomatis* etiology

Test selection

- Culture
 - ◆ Preferred, when available, because of high sensitivity and specificity
 - ◆ EIA, nucleic acid probe, and DFA tests
 - ◆ EIA, nucleic acid probe, and DFA tests that are FDA-cleared for use with conjunctival specimens have had uniformly high sensitivities with conjunctival specimens from newborns; evaluation studies are more limited for conjunctival specimens from adults with conjunctivitis
 - ◆ Specificities of tests on conjunctival specimens have also been high, although the potential for crossreaction with other bacteria exists for EIA and for culture and DFA if used with stains that are not specific for *C. trachomatis*
 - Other tests are not recommended

Source: From ref. 33.

The most common commercial test for *C. trachomatis* is the DNA probe, which uses nucleic acid hybridization to detect chlamydial DNA from urogenital swabs. The DNA probe detects an infection with specimens that have as few as 1000 EBs. It has a sensitivity of 85–90% and a specificity of 98–99% compared to culture, and has a sensitivity of 77–93% compared with NAATs (8). Because the false-positive rates with DNA probes are high, the CDC recommends that positive DNA probe test results in low-prevalence populations be confirmed by a second test (33). One very attractive feature of the DNA probe is that the swab that is used to collect the specimen from the urogenital tract to test for *C. trachomatis* can also be used to test for *N. gonorrhoea*.

Older nonculture diagnostic tests include direct fluorescent antibody (DFA) test and enzyme-linked immunoassay (EIA). DFA detects the outer membrane protein of EB and directly visualizes it with immunofluorescence. The sensitivity of DFA is only about 75%, but it has a specificity of 98%. At least 10 EBs are necessary to detect infection. Clinical skills are required to obtain specimens. The sensitivity of DFA is often reduced by blood on the sample. Today, DFA is used most frequently in the laboratory to confirm positive results of other nonculture tests.

One of the earliest nonculture tests developed was EIA. EIA detects a chlamydia lipoprotein antigen by attaching specific antibodies coupled with an enzyme to the antibody. A color change occurs when the enzyme, which remains after binding with the antibody, acts on a substrate. It takes approximately 10,000 EBs to cause an EIA to turn positive. The EIA has a sensitivity that varies from 62 to 75% and has a specificity of 97%. A major drawback of the older EIAs was that they bound to other Gram-negative organisms as well as *C. trachomatis*, which led to false-positive test results. This problem has been overcome in newer versions by the addition of blocking reagents or by using DFA tests to confirm EIA results. When either of these additional methods is used, specificity is increased to 99%. The antigen detection techniques are generally less expensive and easier to perform than NAATs. However, the antigen detection techniques have a lower sensitivity than NAATs, and they have lower positive predictive values. Therefore, if an antigen detection tests are used to screen a population with a 2–3% prevalence of infection, about half of the results will return falsely positive (an incorrect result). For this reason, routine confirmation is generally recommended for positive cases.

Chlamydial infections can also be diagnosed by culture. The specimen must be cultured in tissue culture because *C. trachomatis* is an obligate intracellular organism and, therefore, is unable to grow on artificial media. Culture allows for antibiotic sensitivity testing as well as genotyping, which may be important for public health reasons. In the past, the sensitivity of culture techniques was thought to be close to 100%. As a result, for many years, the culture was considered the gold standard. Today, however, it is recognized that at least 10–100

organisms are needed to result in a positive culture, but far fewer organisms can be detected by NAATs. Overall, it has been estimated that culture techniques have 65–85% sensitivity compared with NAATs. Tissue cultures cost more than NAATs, are technically difficult and labor-intensive, and take longer for results. However, in many courts, only the result of tissue culture may be introduced as evidence.

Regardless of the exact technology used to test for *C. trachomatis*, good specimen collection techniques are essential. In order to best detect the presence of *C. trachomatis*, infected cells should be collected. The scrapings from the endocervical area or the urethra are more apt to lead to detection of an infection than testing discharge. Using a cytobrush to collect cervical specimens improves the sensitivity of the culture and antigen-detection tests. The cytobrush can safely be used in pregnant women to collect specimens. When urine specimens are to be tested, sensitivity is acceptable only if the first drops of urine are collected, without significant dilution from additional urine. The patient should not have urinated for at least 1 hour before providing the specimen.

Cytology was used to detect chlamydial infections before more sensitive tests were developed. To make the diagnosis, specimens obtained from the genital tract were studied for the presence of inclusion bodies. The sensitivity of cytology testing is very low with only 20% cases being detected. However, NAATs can be used on cervical specimens collected by liquid cytology to detect low levels of chlamydial infection.

Antibodies for *C. trachomatis* can be assayed in serum. Serology for chlamydial antibodies is not useful in detection of acute infection because of poor specificity and reproducibility. In addition, serology and direct evidence of infection are not well correlated (34). Therefore, serology cannot distinguish between active vs resolved infection. Serology may be helpful in assessing if possible tubal factors are a cause of a woman's infertility and help determine who might benefit from hysterosalpingography (35).

SCREENING RECOMMENDATIONS

Targeted screening protocols are needed to control chlamydial infections for several reasons: the prevalence of *C. trachomatis* is relatively high, only a minority of women with chlamydial infections develop symptoms, and the sequelae of infection are potentially serious.

Routine screening of all sexually active women age 26 or younger is recommended whether or not the woman is pregnant. The frequency of subsequent testing of women under age 26 who are in stable mutually monogamous relationships after an initial negative test has not been determined. Screening of older women should be done only if these women are at increased risk (new or multiple

sex partners, a prior history of a sexually transmitted infection [STI] and inconsistent use of condoms in high-risk relationships).

Routine screening of heterosexual men is not recommended, but testing is recommended for symptomatic men and those who are in settings with high prevalence of chlamydia (e.g., adolescent clinics, correctional facilities, and STD clinics). For sexually active MSM, the CDC recommends annual urethral/urine screening for chlamydia and rectal chlamydial cultures for MSM who have had receptive anal sex. The CDC recommends screening every 3–6 months for MSM at highest risk (those with multiple sexual partners, or those who use illicit drugs) (21). Men who are sex partners of infected women or men do not require testing for chlamydia infection before initiation of therapy but might benefit from testing for public health reasons.

It is important to note that screening in low prevalence populations produces high false-positive test results. The positive predictive value using a DNA probe test, performed in a setting with a prevalence of 2%, is under 50%. Because over half of the positive test results are not true positives (the patient is not infected with *C. trachomatis*), a confirmatory test is required. This can be done either by retesting the original specimen automatically in the laboratory using a different testing technology or by performing a second test from the same or a different site in the patient.

DIAGNOSIS

Clinical syndromes, such as nongonococcal urethritis or mucopurulent cervicitis may be diagnosed based on clinical signs and symptoms if supported by microscopic findings of leukocytosis. However, chlamydial infections are often asymptomatic, so diagnosis generally requires chlamydia-specific laboratory test identification/confirmation. Care must be taken, particularly in low-risk patients and patients in low-prevalence populations, to confirm positive test results to reduce the risk of false-positivity.

In the face of laboratory-confirmed diagnosis of chlamydial cervicitis or urethritis, the patient should be evaluated for associated STIs. About 30% of women with chlamydial cervicitis have concomitant trichomonal vaginitis. Gonorrhea accompanies chlamydial infections, but because of relatively low population prevalence, treatment for gonorrhea should await laboratory confirmation in most geographic areas. Other STIs, such as HIV, hepatitis B virus, and syphilis, should be evaluated on the basis of local prevalence rates.

TREATMENT

Because of the unique intracellular characteristics of *C. trachomatis*, only certain antibiotics are effective in treatment. The CDC treatment guidelines for chlamydial infections are summarized in Table 3 (21). Tetracycline and doxy-

Table 3
Chlamydial Infection—CDC STD Treatment Guidelines 2006

| Recommended regimens | Alternative regimens |
|--|--|
| Adolescents and adults | |
| <i>Select one of the following:</i> | |
| Azithromycin ^a 1 g orally once | Erythromycin base ^b 500 mg orally four times a day for 7 days |
| Doxycycline ^c 100 mg orally twice a day for 7 days | Erythromycin 800 mg orally four times a day for 7 days |
| | ethylsuccinate ^b 300 mg orally twice a day for 7 days |
| | Ofloxacin ^d 300 mg orally twice a day for 7 days |
| | Levofloxacin ^d 500 mg orally daily for 7 days |
| Pregnant women | |
| <i>Select one of the following:</i> | |
| Azithromycin 1 g orally in a single dose | Erythromycin base ^b 500 mg orally four times a day for 7 days |
| Erythromycin base 500 mg orally four times a day for 7 days | Erythromycin base ^b 250 mg orally four times a day for 14 days |
| | Erythromycin 800 mg orally four times a day for 7 days |
| | ethylsuccinate ^b 300 mg orally twice a day for 7 days |
| | Erythromycin 400 mg orally four times a day for 14 days |
| | ethylsuccinate ^b 400 mg orally four times a day for 14 days |

^a Safety and efficacy among pregnant and lactating women has not been established (pregnancy category B).

^b Erythromycin is less efficacious than either azithromycin or doxycycline, and gastrointestinal side effects frequently discourage patients from complying with this regimen. Test of cure should be done 3 weeks after completion of treatment with erythromycin.

^c Contraindicated for pregnant and lactating women and for children younger than 8 years old.

Continued on next page

Table 3 (Continued)
Chlamydial Infection—CDC STD Treatment Guidelines 2006

| | |
|---|---|
| <i>Ophthalmia neonatorum</i> caused by <i>C. trachomatis</i> | |
| Erythromycin ^{b,e} base or ethylsuccinate | 50 mg/kg/day orally divided into four doses daily for 14 days |
| <i>Chlamydial infections among children who weigh ≤ 45 kg</i> | |
| Erythromycin ^b base or ethylsuccinate | 50 mg/kg/day orally divided into four doses daily for 14 days |
| <i>Chlamydial infections among children who weigh ≥ 45 kg but who are aged ≤ 8 years</i> | |
| Azithromycin ^a | 1 g orally once |
| <i>Chlamydial infections among children aged ≥ 8 years. Select on of the following:</i> | |
| Azithromycin ^a | 1 g orally once |
| Doxycycline ^c | 100 mg orally twice a day for 7 days |

^a Safety and efficacy among pregnant and lactating women has not been established (pregnancy category B).

^b Erythromycin is less efficacious than either azithromycin or doxycycline, and gastrointestinal side effects frequently discourage patients from complying with this regimen. Test of cure should be done 3 weeks after completion of treatment with erythromycin.

^c Contraindicated for pregnant and lactating women and for children younger than 8 years old.

^d Contraindicated for pregnant and lactating women.

^e An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants younger than 6 weeks who were treated with this drug. Infants treated with erythromycin should be followed for signs and symptoms of IHPS.

cycline inhibit bacterial protein synthesis by blocking the attachment of the transfer RNA-amino acid to the ribosome. Common alternatives to doxycycline are the macrolide antibiotics, erythromycin or azithromycin. Macrolide antibiotics inhibit protein synthesis by binding to the p site on 50S RNA molecule of the bacterial ribosome, blocking the exit of the growing peptide chain. Azithromycin has high tissue penetration levels and a very long half-life, allowing a single dosing regimen. Single-dose therapy enhances compliance and treatment success rates. Clinical cure rates for doxycycline and azithromycin are 96–99% and 97%, respectively (36,37). Resistance to tetracycline and macrolide antibiotics has been reported (38). Single-dose therapy with azithromycin is generally preferred when there is concern that multiple dose therapies will not be completed. In one study of patients prescribed 7-day therapies with doxycycline, only 25% of patients followed instructions completely, 24% took no drug, and the remaining 51% used some intermediate amount of the drug (39).

Quinolone antibiotics act by targeting two enzymes, DNA gyrase and topoisomerase IV, which are necessary for DNA replication. Within this group of antibiotics, ofloxacin and levofloxacin are most effective. *C. trachomatis* has the potential to mutate leading to quinolone resistance when exposed to subinhibitory concentrations of antibiotics (40). Patients should be encouraged to complete all medications for their full course of therapy.

Amoxicillin is no longer recommended for treatment. Other penicillin and all cephalosporin antibiotics have no role in the management of chlamydial infections (41).

Patients should be instructed to abstain from all sexual contact until all of their sex partners have been treated. Treatment is considered complete 7 days after finishing medication. The need for this counseling was highlighted by a study of 597 college women randomized to azithromycin vs doxycycline in which two pregnancies occurred during the 2-week study period (37). Patients should also be counseled on future consistent use of condoms and other safer sex practices.

FOLLOW-UP

It is not necessary to perform a routine test of cure after therapy, except in women treated with erythromycin. It is recognized that erythromycin causes many side effects and that compliance is therefore often poor. Routine repeat testing of all non-pregnant women with chlamydial infection should be considered 3–4 months after treatment. This is particularly important for adolescent women who often return to the same high-risk environment from which they acquired their first infections. Routine repeat testing is also encouraged at every other examination done 3–12 months after treatment regardless of whether the patient believes that her sex partner(s) was treated.

COMPLICATIONS OF INFECTION

Infertility, ectopic pregnancy and pelvic pain are sequelae of both symptomatic and asymptomatic PID. In women with confirmed PID, infertility was seen in 16 vs 2.7% of controls. Ectopic pregnancy was 9.1 vs 1.4% and tubal factor infertility was 10.8 vs 0% (42). The risk of infertility increases with number of episodes and severity of the inflammation. In women who had had PID, hospital readmissions for abdominal and pelvic pain was significantly more likely and the risk for hysterectomy was six times greater than controls (43). Chronic pelvic pain after PID is associated with reduced physical and mental health (44).

PARTNER NOTIFICATION AND REPORTING REQUIREMENTS

Chlamydia is a reportable disease in all 50 states. All sexual contacts for the 60 days prior to onset of symptoms (or diagnosis of asymptomatic infections) should be evaluated, tested, and treated. It is important to note that it is *not* necessary to await positive test results for chlamydial infection to initiate partner therapy; therapy for chlamydial infection should be given to partners on an epidemiological basis. Treatment for other possible STIs not detected in the index case should await laboratory confirmation.

If there is a concern that a heterosexual sex partner will not seek care, the CDC suggests that the patient can provide the partner the treatment. In California, state law allows clinicians to treat sex partners of patients found to have laboratory-confirmed genital chlamydial infections without co-infection with gonorrhea or other complications. Under this law, treatment for chlamydia can be given without any contact or evaluation, even if the partner is not a patient of the clinician. This provision (patient-delivered partner therapy) is generally reserved for partners who are not expected not to seek care for the problem. The recommended treatment is azithromycin. Specialized instructions that explain the reason for the treatment and screen for macrolide allergy (e.g., erythromycin) accompany the medications. Also included in the packet is encouragement to seek professional care to be evaluated for other (as yet undiagnosed) STIs. Recently, research has demonstrated again that expedited treatment with patient-delivered partner therapy reduced the rates of persistent or recurrent gonorrhea and chlamydial infection, but gonorrhea reduction was more significant than chlamydia reduction (45). Patient-delivered partner therapy is not recommended for MSM because of the high risk of coexisting infections in that partner, especially HIV.

PREGNANCY-RELATED ISSUES

The association between chlamydial cervicitis and preterm rupture of membranes, preterm labor, and preterm delivery has been strongly suggested by two clinical trials, which served as a basis for CDC recommendation for screening in

pregnancy (46,47). However, no prospective placebo-controlled studies have verified this association. Given the strength of the association found in these earlier studies, however, it may not be ethical to conduct placebo-controlled trials. The role *C. trachomatis* plays in the etiology of postpartum endometritis is controversial, but the diagnosis should be considered when women present 2–3 weeks postpartum with fever, chills, purulent lochia, and a tender, boggy, enlarged uterus. Women infected with *C. trachomatis* at delivery were more likely to experience febrile complications after postpartum tubal ligation (48). The association of chlamydial cervicitis and postabortal infection is clear. Estimates are that 10–35% of women who undergo elective abortion with chlamydial cervicitis will develop postabortal endometritis/PID. This observation has led to the practice of routine antibiotic prophylaxis at the time of surgical abortion.

In pregnancy, the optimal testing scheduled has not been established but the CDC recommends testing prenatal patients under 25 and other high-risk women depending on local prevalence rates. Early testing could reduce pregnancy risks associated with infection, such as low birth weight and premature delivery. Testing late in pregnancy can decrease transmission to the infant and diminish the risk of postpartum maternal infections. Combined testing has not been evaluated.

Doxycycline should not be used in pregnancy. In pregnant women, test of cure is routinely recommended by the CDC, although some experts do not deem it necessary if the patient was treated with azithromycin. It is important to wait 3 weeks from the completion of therapy to do test of cure, because some tests may detect *C. trachomatis* remnants even after the organisms have been eradicated. Infected women should be retested in the third trimester.

PREVENTION

A National Institutes of Health panel performed a comprehensive review of the literature in 2000 and concluded that there was not sufficient evidence to allow an accurate assessment of the degree of protection against chlamydia offered by correct and consistent condom use (*see* Chapter 15) (49). The CDC now recommends condom use to reduce the spread of chlamydia (50). A recent study with a case-crossover design suggested that correct and consistent condom use was associated with a 50% reduction in chlamydial infection. The investigators were also able to indentify a dose–response relationship.

In 2004, a review of studies published after the NIH conference found that the literature in that time period supported the conclusion that condom use was associated with a statistically significant protection for men and women from chlamydia infections (51). An analysis of 45 studies published between 1966–2004 concluded that most studies found that condom use was associated with a reduced risk of chlamydia in both men and women (52).

CASE STUDY

Robert calls your office because a short-term female partner notified him that he has been exposed to chlamydia. He says that she gave him four antibiotic tablets to take, but he did not use this medication yet because he has no symptoms. He takes tetracycline 250 mg daily for acne treatment. He wants to know if it is safe to take these tablets.

Questions

1. What pills did his partner give him?
2. Should he be treated without any other evaluation?
3. Should he be treated without a test showing that he is infected?
4. Will his daily tetracycline be adequate therapy?
5. What if he says that he used condoms when he had sex with her?

Answers and Teaching Points

1. California allows providers to give patients who have chlamydial cervicitis azithromycin to treat their partners, especially if the woman doubts her partner will seek professional care. This is called patient-delivered partner therapy.
2. Robert should be advised that he needs to be seen immediately and tested for related STIs. All anatomical sites where he had sexual contact with her should be tested. All of his subsequent sexual contacts need testing and treatment.
3. Robert should take the azithromycin therapy based only on his partner's infection.
4. His tetracycline dose is too low to provide treatment for his chlamydial infection.
5. If he used condoms before any genital contact with the infected woman, his treatment may be held awaiting the test results unless he had other sexual contact with her not protected by condoms.

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