Chlamydia

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Disease Type 1: Pathogen-Based Diseases
Disease 4: Chlamydia

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Epidemiology in the United States

Incidence

Chlamydia is the most common reportable bacterial sexually transmitted infection (STI) in the United States, with more than 1.5 million cases reported in 2015. [1] Since many persons with chlamydial infection may have minimal or no symptoms, the actual number of annual infections is significantly higher than the reported cases. [2] The number of reported chlamydia cases have significantly increased since the early years of reporting that began in the 1980’s (Figure 1), [1] which may reflect an increase in the number of true infections, enhanced screening with more sensitive diagnostic tests, or a combination of both. Chlamydial rates of reported cases have consistently been higher in women than in men (Figure 2), with the highest rates (reported cases per 100,000 population) among among females 15 to 24 years of age (Figure 3). [3] In the United States, racial and ethnic minorities are disproportionately affected by chlamydia, particularly blacks (Figure 4). [1] Factors contributing to these inequities may include differential access to quality health care, social and economic conditions, and higher prevalence of disease in sexual networks, and differences in immunogenetic determinants that influence the immune response to chlamydia. The South has consistently had the highest rate of reported cases, although the difference between the rate in the South and other regions is small (Figure 5). [1] The three states with the highest rates are Alaska, Louisiana, and North Carolina; of note, the rate in Washington DC is higher than any state (Figure 6). [1]

Prevalence

Based on National Health and Nutrition Examination Surveys (NHANES), chlamydia prevalence in the U.S. is estimated to be 1.5%. [4] Chlamydia prevalence is highest among adolescents and young adults, as well as among racial and ethnic minorities. Test positivity is often used as a proxy of chlamydia prevalence in a population. During 2007 to 2012, chlamydia test positivity among males and females aged 14 to 39 was 1.7%. [1] Among sexually active females aged 14 to 24 years (the population targeted for routine screening), chlamydia prevalence was 4.7%; black females had, by far, the highest prevalence (Figure 7). [1]

Risk Factors

Risk factors associated with acquisition of chlamydial infection include new or multiple sex partners, a history of STIs, presence of another STI, and lack of barrier contraception. [5] The presence of columnar epithelial cells on the ectocervix, referred to as ectopy, is a condition that may increase susceptibility to chlamydial infection; oral contraceptive use contributes to ectopy. [6] Adolescents and young adults are at increased risk for chlamydial infection for a combination of biological, behavioral, and cultural reasons, including difficulty accessing preventive health care services for STIs.
Impact

Chlamydia is the most common non-viral STDs and the most significant contributor to cost, with total lifetime direct medical costs estimated at $516.7 million.[5,7,8,9] Although diagnosis and management of chlamydia is costly, untreated genital chlamydia infections can result in major complications for women, including pelvic inflammatory disease, chronic pelvic pain, fallopian tube scarring, and infertility.[10,11] In addition, studies have shown that rectal chlamydia infection in men who have sex with men significantly increases the risk of HIV acquisition[12]. Screening for rectal chlamydia in men who have sex with men can be a cost-effective intervention for HIV prevention.[13]
**Microbiology and Pathogenesis**

**Organism and Classification**

*Chlamydia trachomatis* is an obligate intracellular bacterium with a cell wall and ribosomes similar to those of gram-negative organisms.[14] The *C. trachomatis* cell wall is unique in that it contains an outer lipopolysaccharide membrane, but it lacks peptidoglycan; within the cell wall, cysteine-rich proteins act as the functional peptidoglycan equivalent. The absence of peptidoglycan explains why the organism is not seen with standard Gram’s staining and why beta-lactam antimicrobials are not effective for treatment. *C. trachomatis* is a member of the *Chlamydiaceae* family. The genus *Chlamydia* includes three species that infect humans: *C. trachomatis*, *C. pneumoniae*, and *C. psittaci*. The species *C. trachomatis*, which exclusively infects humans, can cause (1) trachoma in persons of all ages, (2) anogenital infections, lymphogranuloma venereum (LGV), and conjunctivitis in adults, and (3) conjunctivitis and pneumonia in neonates.

**Life Cycle**

*C. trachomatis* typically infects columnar epithelial cells at mucosal sites, often becoming a chronic infection that may last months or even longer than a year if untreated. *Chlamydia trachomatis* has a complex reproductive cycle, typically requiring 48 to 72 hours to complete.[15,16] The organisms replicate within a host cell, eventually causing death of the host cell.[17] The life cycle of *C. trachomatis* involves five key steps (Figure 8):

1. The elementary body, a small, infectious, but non-replicating particle found in secretions, attaches to and enters a host cell, such as an endocervical or urethral columnar epithelial cell. The contact with the host cell membrane causes the elementary body to induce its own endocytosis.
2. Within eight hours, the now-intracellular elementary body interacts with glycogen and transforms into a reticulate body, which begins to multiply within an isolated intracellular structure referred to as an inclusion. The reticulate bodies are the non-infectious replicating form.
3. Within 48 hours, some of the reticulate bodies begin to reorganize back to elementary bodies.
4. Within 72 hours, most of reticulate bodies have transitioned back to elementary bodies and the inclusion either undergoes lysis at the host cell wall or the intact inclusion (containing numerous elementary bodies) is released into the extracellular space.
5. Regardless of whether the inclusion undergoes lysis or is extruded intact, the elementary bodies are released to infect adjacent cells or to be transmitted to and infect another person.

**Transmission**

Sexually-acquired *C. trachomatis* is highly transmissible, with chlamydial infection rates between sexual partners reported of approximately 55%, with a per-act transmission risk of about 10%.[18] Sexual transmission rates per sex act are thought to be slightly higher from men-to-women than from women-to-men, but given the number of asymptomatic carriers in the general population, estimates for the rate of transmission remain imprecise. Transmission of *C. trachomatis* can also occur from mother-to-infant via the genital tract during birth.
Clinical Manifestations

The type of clinical infection caused by *C. trachomatis* is determined by the outer membrane protein A (OmpA—also known as MOMP), which can be determined based on culture (i.e., OmpA serovar) or molecular methods (i.e., OmpA genotype). Genital, rectal, oropharyngeal, and conjunctival infections are usually caused by *C. trachomatis* serovars D through K (as is conjunctivitis and pneumonia in neonate), trachoma by serovars A through C, and lymphogranuloma venereum (LGV) by serovars L1-L3. Although the majority of *C. trachomatis* infections caused by OmpA types D through K in women and men are asymptomatic, symptoms and clinical syndromes can develop at any site of infection. In patients who develop symptomatic infection, the incubation period for *C. trachomatis* infection is estimated to be 7 to 21 days. *C. trachomatis* can cause a range of clinical syndromes, including urethritis in males and females, cervicitis, proctitis, and conjunctivitis in both adults and neonates, and pneumonia in neonates.

Genital Infection in Men

In men, *C. trachomatis* can cause an array of genitourinary clinical manifestations. Complications are uncommon in men, but they can occur and manifest as epididymitis or reactive arthritis.

Urethritis

The most common site for chlamydial infection in heterosexual men is the urethra. Although most men identified with urethral chlamydial infection have no symptoms, some will develop dysuria and urethral discharge, which is clear, mucoid, or mucopurulent; the clinical presentation is typically referred to as non-gonococcal urethritis.[19] Although attempts to distinguish gonococcal urethritis from non-gonococcal urethritis on clinical examination are not reliable, the discharge from urethritis caused by *C. trachomatis* tends to be a mucopurulent, mucoid, or clear, rather than a purulent discharge as often occurs in men with gonococcal urethritis.

Epididymitis

In males, epididymitis is the most common local complication of *C. trachomatis* infection and patients typically develop signs and symptoms that include unilateral scrotal pain, epididymal swelling, and tenderness at the affected region.[20] For patients with epididymitis that have a concomitant urethral discharge, most have evidence of urethritis on a Gram’s stain of a urethral discharge specimen, but the chlamydia organisms are not visible on Gram’s stain. Up to 70% of sexually transmitted cases of epididymitis are due to *C. trachomatis*; infection with *N. gonorrhoeae* can also cause epididymitis.[20]

Genital Infections in Women

The majority of women with chlamydial infection initially have no signs or symptoms, but may present later with uncomplicated infection (cervicitis or urethritis); some women develop complicated infections, including pelvic inflammatory disease, perihepatitis, endometritis, salpingitis, or reactive arthritis.

Cervicitis

The cervix is the site of infection in 75% to 80% of chlamydia-infected women. Cervicitis is asymptomatic in most cases. In asymptomatic women, clinical examination of the cervix usually will not distinguish between women infected with chlamydia and uninfected women, due to the infrequency of finding cervicitis (cervical findings of mucopurulent endocervical discharge and/or spontaneous or easily induced endocervical bleeding). When symptoms are present, they can be nonspecific, such as vague discomfort or spotting. Signs on pelvic examination may include mucopurulent endocervical discharge and spontaneous or easily-induced endocervical
Causes of mucopurulent cervicitis other than *C. trachomatis* include *N. gonorrhoeae* and less frequently *M. genitalium*.

**Urethritis**

Urethral infection with chlamydia in women is usually asymptomatic, but it can cause “dysuria-pyuria” syndrome, or an “acute urethral syndrome”, mimicking acute cystitis. Symptoms may include dysuria and urinary frequency, especially in young women with a recent, new sex partner. Since women with symptomatic chlamydia urethritis have a clinical presentation similar to women with urinary tract infection, the potential exists to miss the diagnosis of chlamydia if testing is not performed in this setting, which will likely result in untreated chlamydia as most treatments for urinary tract infection will not effectively treat chlamydia.

**Pelvic Inflammatory Disease**

Women with *C. trachomatis* infection can develop pelvic inflammatory disease (PID), which is a subclinical to acute clinical syndrome associated with the ascending spread of microorganisms from the cervix to the endometrium, fallopian tubes, ovaries, and contiguous structures. Although the majority of women with PID have subclinical infection, some present with lower abdominal pain along with bimanual findings of cervical motion tenderness, with or without uterine or adnexal tenderness.[11,23] Chlamydia-associated PID can result in tubal scarring that may cause tubal factor infertility and increase the risk for ectopic pregnancy. An estimated 10 to 15% of women with untreated chlamydia can develop PID. About 20% of women treated for PID become infertile, 30% develop chronic pain, and about 1% of women who conceive have an ectopic pregnancy.[24] The extensive long-term morbidity associated with chlamydial infection underscores the importance of aggressive prevention, screening, and treatment programs.[5,25]

**Perihepatitis (Fitz-Hugh-Curtis Syndrome)**

Untreated pelvic infection in women with *C. trachomatis* can cause inflammation of the liver capsule, which is commonly referred to as perihepatitis or the Fitz-Hugh-Curtis Syndrome.[26,27] Although perihepatitis was initially attributed only to gonococcal infection, it is now known to be more often associated with chlamydial infection. Perihepatitis is characterized by right upper quadrant pain, nausea, vomiting, and fever, which are generally accompanied by evidence of PID on physical examination.[28]

**Manifestations Seen in Men or Women**

**Conjunctivitis**

Infection of the eye with *C. trachomatis* can occur in adults as a result of autoinoculation from secretions from another site of infection, such as the genital tract. The signs and symptoms are unilateral eye discomfort with hyperemia. The secretions may be mucopurulent, but are more typically clear to cloudy.

**Oropharyngeal Infection**

Oropharyngeal infection with Chlamydia trachomatis most frequently is asymptomatic in both men and women.[29] It can also present as acute tonsillitis, acute pharyngitis or abnormal pharyngeal sensation syndrome. When clinical signs and symptoms are described, the presentation can range from minimally symptomatic disease (i.e. dry or pruritic throat) to exudative tonsillopharyngitis. Chlamydial tonsillopharyngitis is marked by generalized pharyngeal and tonsillar hyperemia with possible addition of swollen anterior pillars and uvula, as well as diffuse purulent exudate on the tonsils.[30]
**Proctitis and Proctocolitis**

Infection with *C. trachomatis* OmpA types D through K in the rectal region is usually asymptomatic, but can lead to proctitis or proctocolitis, which can manifest as rectal pain, mucoid or hemorrhagic discharge, fever, and/or tenesmus.[31] Diagnosis can be supported via anoscopy findings (mucopurulent discharge, pain, and spontaneous or induced bleeding). This infection can occur in men or women practicing receptive anal intercourse. Women may also be infected rectally as a result of local spread of the infection from cervical secretions. Rarely, chronic infections can cause scarring and fistula formation. LGV more often presents as proctitis or proctocolitis, and therefore additional diagnostic methods are required to differentiate LGV from non-LGV strains of *C. trachomatis*.[32,33]

**Lymphogranuloma venereum (LGV)**

LGV is caused by *C. trachomatis* serovars L1, L2, or L3; it is an uncommon infection in the United States, but sporadic cases and outbreaks have been reported among MSM, most of whom have HIV infection. Although most cases of LGV in the United States are rectal infections, LGV can present with a distinct genital infection syndrome. Signs and symptoms include multiple, enlarged, matted, tender inguinal lymph nodes that may be suppurative and are usually bilateral. Systemic signs and symptoms, such as fever, chills, or myalgia, also may be present.[32] A self-limited genital ulcer sometimes occurs at the site of inoculation. Specimens from genital sites and lymph nodes can be obtained in an attempt to identify *C. trachomatis* by a nucleic acid amplification test. Nucleic acid testing does not distinguish standard strains of *C. trachomatis* from LGV strains. The duration of therapy is longer for infections caused by LGV strains (21 days) versus non-LGV chlamydia strains (7 days).[1]

**Reactive Arthritis**

Reactive arthritis, previously referred to as Reiter’s syndrome, is a post-inflammatory autoimmune disease that can result from urogenital chlamydia infection. The characteristics of the syndrome include conjunctivitis, urethritis, oligoarthritis, and skin lesions (keratoderma blennorrhagica) and circinate balanitis (Figure 9). Some studies have reported the presence of chlamydia antigens and DNA within the joints.[34] This complication infrequently occurs, but when it does, the onset is typically 3 to 6 weeks after urogenital chlamydia infection and it can occur even in persons who receive effective treatment for chlamydia infection. Reactive arthritis affects predominantly males, particularly those positive for HLA-B27, and it usually resolves within 3 to 6 months. Reactive arthritis may not respond to antimicrobial treatment, but symptoms usually respond to non-steroidal anti-inflammatory agents.

**Chlamydial Infections in Infants and Children**

Although chlamydial infections are now seen infrequently among infants and children in the United States, they must still be considered in the scenario of inadequate prenatal care. Among cases of perinatal chlamydial infection, the most common presentation is inclusion conjunctivitis, which occurs in about 25% of neonates born to mothers who have untreated cervical chlamydia infection. The second most common manifestation is neonatal pneumonia and this occurs in only about 10 to 15% of infants of mothers who have untreated cervical chlamydia.

**Conjunctivitis**

For infants, conjunctivitis is the most common clinical condition resulting from perinatal transmission of chlamydia. Ocular infection with *C. trachomatis* results from exposure of the neonate to infected secretions from the mother’s genital tract during birth and the exposure may also involve mucous membranes of the oropharynx, urogenital tract, and rectum. Inclusion conjunctivitis occurs 5 to 14 days after delivery. The signs range from mild scant mucoid discharge to severe copious purulent
discharge, chemosis, pseudomembrane formation, erythema, friability, and edema. Neonatal ocular prophylaxis with silver nitrate solution or antibiotic ointments for prevention of gonorrhea transmission does not prevent perinatal transmission of *C. trachomatis* from mother to infant. A chlamydial etiology should be considered for all infants aged 30 days or under who have conjunctivitis.

**Trachoma**

Trachoma is the leading cause of preventable blindness in the world and is caused primarily by *C. trachomatis* serotypes A, B, Ba, and C. Trachoma is found in select regions of the world, mostly in the Middle East and Southeast Asia. The disease is most often contracted person-to-person through hand (or fomite) contact with an infected eye, followed by autoinoculation. Most cases of trachoma occur in the setting of poor sanitary conditions and some cases result from fly transmission. Trachoma is not an STD. The process begins as a follicular conjunctivitis, which, if untreated, progresses to an entropion wherein the eyelid turns inward and lashes ulcerate the corneal surface over time. The disease is diagnosed clinically and treatment with single-dose azithromycin is usually effective. This disorder is not a sexually transmitted disease and it is not transmitted from mother-to-child during birth.

**Pneumonia**

Chlamydia pneumonia in infants occurs 4 to 12 weeks after delivery. Notably, infection of the nasopharynx is thought to be a precursor condition that is usually asymptomatic, but can progress to pneumonia. The signs are cough, congestion, and tachypnea. Infants are usually afebrile, and rales are apparent with auscultation of the lungs.

**Urogenital Infection**

Urogenital infections in preadolescent males and females are usually asymptomatic and can be the result of vertical transmission during the perinatal period. Genital or rectal infection can persist for as long as two to three years, so infection in young children may be the result of perinatally-acquired infection. Sexual abuse is a major concern when chlamydia (or any STI) is detected in preadolescent males or females. The STI evaluation in a case of suspected abuse should be performed by, or in consultation with, an expert in the assessment of child sexual abuse. Only tests with high specificity should be used because of the legal and psychosocial consequences of a false-positive diagnosis.
Laboratory Diagnosis

The selection of a laboratory test to detect the presence of *C. trachomatis* is a critical component of disease management and prevention.[33] The testing technology has shifted from culture-based methods to molecular-based techniques and this represents a substantial improvement in test sensitivity and ease of specimen collection.

**Nucleic Acid Amplification Tests (NAATs)**

NAATs amplify nucleic acid sequences (either DNA or RNA) that are specific for the organism being detected. Similar to other non-culture tests, NAATs can detect live or non-viable organisms. *C. trachomatis* NAATs are FDA-cleared for use on urine specimens from men and women, urethral swabs in men, and endocervical swabs in women; some tests are cleared for vaginal swabs.[2] The use of *C. trachomatis* NAAT for pharyngeal and rectal specimens is not FDA approved; however, laboratories can perform certain validation procedures, such as Clinical Laboratory Improvement Amendment (CLIA)-defined performance specifications, to enable them to test specimens for clinical purposes. In men, NAATs are the most sensitive and recommended test for detecting *C. trachomatis* from a urethral swab or first-catch urine specimen.[2] For chlamydia screening in women, vaginal swabs are preferred over urine samples and several studies have shown that self-collected vaginal swabs are preferred by women and perform equal to or better than clinician-collected vaginal swabs.[37, 38, 39, 40, 41] In addition, in men and women, self-collected rectal swabs for NAAT has also performed well.[42] There is currently insufficient evidence to support the use of self-collected oropharyngeal or penile meatal swabs for the diagnosis of chlamydia.[2] Multiple NAATs are commercially available for the detection of *C. trachomatis*.

**Non-amplification Molecular Tests**

Molecular tests that do not use nucleic acid amplification encompass a variety of antigen detection and nucleic acid hybridization methods. These include enzyme-immunoassays (EIA), direct fluorescent antibody tests (DFA), and nucleic acid hybridization tests, a distinct non-NAAT methodology that detects *C. trachomatis*-specific DNA or RNA sequences in rRNA, genomic DNA, or plasmid DNA. All have significantly lower sensitivity (range 50% to 75%) than NAATs.[43] These non-amplification tests are rarely used in clinical practice and they are classified as “not recommended” by the CDC.[2]

**Culture**

Historically, cell culture to detect *C. trachomatis* was the most sensitive and specific method available to detect chlamydial infection. Cell culture, however, is technically complex, expensive, difficult to standardize, and has a lower sensitivity than amplification tests (50% versus 80%). In addition, performing *C. trachomatis* cell culture requires collection of columnar cells from relevant anatomical site(s) and use of stringent transport requirements. The excellent sensitivity and specificity of the NAAT has led to its use in place of culture for most clinical situations; the use of culture for *C. trachomatis* is limited to evaluation of suspected cases of sexual assault in children.

**Serology**

Serologic testing is rarely used to diagnose uncomplicated genital infections caused by *C. trachomatis* because chlamydia serologic tests do not reliably distinguish current from prior infection. Two main types of serologic tests are used for diagnosis: (1) chlamydia complement fixation test (CFT), which measures antibody against group specific lipopolysaccharide antigen, and (2) micro-immunofluorescence (MIF).[33] Serology may be of value in the diagnosis of LGV because many clinicians do not have access to OmpA serotyping or genotyping. Complement-fixation titers of 1:64 or greater can support the diagnosis of LGV in the appropriate clinical context.[44] The more
sensitive and species-specific MIF has replaced the CFT. High background prevalence and infrequent rises and falls in IgG and IgM make it less practical to use as a diagnostic test for uncomplicated genital chlamydial infection. Serology may be useful in evaluation of inguinal LGV and selected chlamydia complications (e.g., perihepatitis and infertility).

**Diagnostic Evaluation in Suspected Sexual Abuse in Children**

Due to high specificity, culture has retained a role in the work-up of suspected sexual abuse in children. NAATs can be used for vaginal and urine specimens, although data are insufficient to recommend the use of NAAT in boys. Chlamydial culture remains the preferred technique for evaluation of *C. trachomatis* infection from all sites in boys and extra-genital sites in girls as part of any sexual assault evaluation. If sexual abuse is suspected, specimens for chlamydia cultures should be collected from the anus (for boys and girls) and from the vagina of girls. All specimens should be retained for additional confirmatory testing. Other nonculture tests (e.g., DFA) are not recommended in this setting because of poor specificity. Insufficient data are available regarding the use of NAATs for extragenital specimens in boys or girls; thus, in this setting, culture remains the preferred method for detecting chlamydia from extragenital sites.

**Reporting Requirements**

Laws and regulations in all states require that persons diagnosed with chlamydia be reported to public health authorities by clinicians, laboratories, or both.
Screening for Infection

Screening for chlamydia in asymptomatic persons has been found to significantly reduce the incidence of chlamydia-associated PID.\[25,45,46\] In general, routine screening for chlamydia should utilize NAAT as the diagnostic test; the United States FDA has cleared NAATs for chlamydia testings on (a) male and female urine samples, (b) clinician-collected endocervical, vaginal, and male urethral samples, and (c) self-collected vaginal swabs if obtained in a clinical setting. Routine oropharyngeal screening for *C. trachomatis* infection is not recommended, primarily because of the low prevalence of oropharyngeal *C. trachomatis* infection. Although chlamydia NAATs for chlamydia are not FDA cleared for rectal samples, the CDC and US Preventive Services Task Force (USPTF) note that chlamydia NAAT can be used on rectal swabs in persons who engage in receptive anal intercourse. The following summarizes the CDC and US Preventive Services Task Force recommendations for routine chlamydia screening.\[2,5,47\]

- **Heterosexual Women:** The high frequency of asymptomatic infection among young women combined with greater risk for morbidity, led to the recommendation by the CDC and the U.S. Preventive Services Task Force (USPSTF) that all sexually active females younger than 25 years of age undergo annual screening for chlamydial infection. More frequent screenings may be appropriate for sexually active adolescents and women with recent *C. trachomatis* infections. In addition, women 25 and older should undergo routine screening if they are considered to have increased risk for chlamydial infection, such as a new partner, more than one sex partner, a sex partner with concurrent (overlapping) partners, or a sex partner who has been diagnosed with an STI.
- **Pregnancy:** At the first prenatal visit, screen all pregnant women younger than 25 and those with increased risk of acquiring chlamydial infection. Rescreen during the third trimester for women younger than 25 and those with increased risk of acquiring chlamydial infection.
- **Women who have Sex with Women:** Recommendations state that same-sex screening should be the same as for heterosexual women.
- **Heterosexual Men:** Routine screening for chlamydial infection is not recommended for heterosexual men. Consider screening for chlamydia in sexually active young heterosexual males in populations with a high prevalence of chlamydia, including those seen at adolescent clinics, correctional facilities, and STD clinics.
- **Men who have Sex with Men:** For sexually active men who have sex with men, routine screening of exposed genital and rectal sites should be performed at least annually, regardless of a history of condom use during sexual exposure. More frequent screening at 3 to 6 month intervals is indicated for men who have sex, including those with HIV infection, if risk behaviors persist or their sexual partners have multiple partners.
- **Persons with HIV Infection:** For individuals with HIV infection who are sexually active, routine screening should be performed at the initial evaluation and at least annually thereafter (more frequent screening may be indicated based on risk).
- **Correctional Facilities:** Routine screening should be performed for women 35 and younger and men younger than 30 at intake.
**Treatment**

**Adolescents and Adults with Urogenital Chlamydia Infections**

The 2015 CDC STD guidelines recommend treatment of urogenital chlamydial infections with either azithromycin $1\,\text{g}$ orally as a single dose or doxycycline $100\,\text{mg}$ orally twice daily for seven days (Table 1).[2] Most studies show comparable efficacy between these two regimens.[48, 49] Generic doxycycline has recently undergone a significant price increase which may be a factor for some patients. Azithromycin has the additional advantage of enabling the provision of single dose directly observed therapy when patient adherence is in question, though there are data showing adequate clinical outcomes despite imperfect adherence with doxycycline.[50, 51] The alternative regimens recommended by the CDC are used only for patients with allergies or adverse reactions to first-line agents, since available data indicate there is no clinically significant emergence of azithromycin or doxycycline drug resistance among $C.\,\text{trachomatis}$ strains.[2, 52] Rectal chlamydial infections are treated similarly to urogenital infection with the caveat that data from observational trials suggest doxycycline may have greater efficacy than azithromycin for the treatment of rectal $C.\,\text{trachomatis}$ infection.[53, 54, 55, 56, 57]

**Adults with Oropharyngeal Chlamydial Infections**

The clinical significance oropharyngeal $C.\,\text{trachomatis}$ infection remains unclear and routine screening for oropharyngeal $C.\,\text{trachomatis}$ infection is not recommended. Since oropharyngeal $C.\,\text{trachomatis}$ can be transmitted to genital sites of sexual partners[58, 59], detection of $C.\,\text{trachomatis}$ from on oropharyngeal sample warrants treatment with either azithromycin $1\,\text{g}$ orally as a single dose or doxycycline $100\,\text{mg}$ orally twice daily for seven days.[2]

**Management of Sex Partners**

For patients diagnosed with urogenital chlamydial infection, all sex partners with whom they had sexual contact in the preceding 60 days should be referred for evaluation, testing, and presumptive treatment with a drug regimen effective against chlamydia.[2] In addition, the most recent sex partner should be evaluated and treated even if the time of the last sexual contact was greater than 60 days before the patient's onset of symptoms.

**Use of Expedited Partner Therapy**

In settings where prompt referral and treatment of sex partners is unavailable or impractical, medical providers should consider use of expedited partner therapy (EPT). This strategy has been demonstrated to decrease the rate of recurrent or persistent chlamydia infection.[60, 61, 62] Use of EPT entails provision of appropriate antibiotics to treat chlamydia, as well as educational and pharmacy information for the partner. The documentation should include notification that partner(s) have been exposed, information about the importance of treatment, signs and symptoms of potential complications, as well as possible therapy-related allergies and adverse effects. Use of EPT is not recommended for men who have sex with men given the significant rate of concurrent infections, such as syphilis and HIV.[2] In addition, use of EPT is contraindicated when there is suggestion by history of PID in a female partner. Finally, EPT is not legal in all states; the CDC maintains an updated information page Legal Status of Expedited Partner Therapy that identifies the legal status of EPT in each state in the U.S., as well as providing links to each state for more detailed state policies.

**Resumption of Sexual Activity**

Patients should be instructed to abstain from sexual intercourse for seven days after a single dose of azithromycin or until completion of a seven-day regimen of doxycycline; in addition, they should not
resume sexual activity until all symptoms related to the chlamydial infection have resolved and their sex partners have received treatment for chlamydia.[2]

**Post-Treatment Follow-Up**

The CDC does not recommend routine test-of-cure after completing therapy for chlamydia in nonpregnant patients, but all women and men should return for repeat testing approximately 3 months after receiving treatment for chlamydia due to the substantial risk of reinfection during the 3-month period following initial diagnosis of chlamydial infection.[2]

**Chlamydial Infections During Pregnancy**

The recommended regimen for chlamydial infections in pregnant women is azithromycin 1 g orally in a single dose.[2,63,64,65,66] Doxycycline is pregnancy category D because of potential toxicity for fetal bone development and possible discoloration of teeth in the unborn baby; doxycycline is not recommended to treat chlamydial infections in pregnancy. Erythromycin estolate is contraindicated during pregnancy because of hepatotoxicity risk. The alternative regimens in pregnancy are amoxicillin, erythromycin base, or erythromycin ethylsuccinate (Table 2).[2] Pregnant women should have a test-cure performed 3 weeks after completion of therapy. Women younger than 25 years and those at increased risk for chlamydial infection also should be retested during the third trimester.

**Neonates with Ophthalmia Neonatorum**

A specific diagnosis of *C. trachomatis* infection in the neonate confirms the need for treatment not only for the neonate, but also for the mother and her sex partner(s). The recommended regimen for the neonate is erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days (Table 3).[2] An association between oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants less than 6 weeks of age who were treated with this drug.[67,68] Thus, infants treated with erythromycin should be followed for signs and symptoms of infantile hypertrophic pyloric stenosis.[69] Data on the use of other macrolides (azithromycin and clarithromycin) for the treatment of neonatal chlamydial infection are limited. The results of one small study suggest that a short course of azithromycin, 20 mg/kg/day orally, one dose daily for three days may be effective. This regimen is considered a recommended alternative to erythromycin. However, use of azithromycin in the neonatal period has also been associated with a higher risk infantile hypertrophic pyloric stenosis, particularly if given in the first 2 weeks of life.[69,70]

**Infant Pneumonia**

For infants with pneumonia caused by *C. trachomatis*, the recommended treatment is a 14-day course of erythromycin base or erythromycin ethylsuccinate; azithromycin, which is much easier to administer and requires only a 3-day course, is considered an alternative regimen (Table 4).[2]

**Infants Born to Mothers Diagnosed with Chlamydial Infection**

Routine use of erythromycin eye ointment given at birth does not prevent neonatal chlamydial infection. Prophylactic antibiotic treatment for infants born to mothers who have an untreated chlamydial ophthalmia is not indicated. Instead, the STD guidelines recommend monitoring the infant for signs and symptoms of chlamydial infection and promptly evaluating and treating any documented infection.[2] Implementation of systematic screening and treatment of pregnant women for *C. trachomatis* is the most effective strategy for reducing perinatal chlamydial infection in the United States.

**Chlamydial Infections in Infants and Children**
The treatment of infants and children with chlamydia is stratified into three groups: younger than 8 years of age and weight less than 45 kg, (2) younger than 8 years of age and weight 45 kg or greater, and (3) age 8 or older (Table 5). In children, the preferred treatment of chlamydial infections (other than ophthalmia neonatorum) is with erythromycin base or erythromycin ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days.[2] Alternative regimens include azithromycin and for children older than 8 years of age doxycycline. The 2015 CDC guidelines recommend that a culture should be obtained at a follow-up visit approximately 2 weeks after treatment is completed to detect therapeutic failure and ensure treatment effectiveness.[2] Use of NAATs for the 2-week follow-up test is inappropriate due to false-positive results from residual C. trachomatis nucleic acids at 2 weeks post-treatment.[33]

Management of Mothers and Their Sex Partners

For neonates or infants diagnosed with chlamydial infection, it is important the mothers and their sex partners undergo diagnostic evaluation and receive empiric treatment for chlamydial infection.
Patient Counseling and Education

Clinicians should use any opportunity to highlight the high importance of routine chlamydia screening in women as a means of preventing chlamydia-related complications in women. This is imperative for sexually active females aged 14 to 24 years amongst whom chlamydia prevalence was 4.7% from 2007 to 2012. Many men and women do not understand the significance and frequency of asymptomatic infection and education will likely increase adherence with routine screening schedules. Patient counseling and education should additionally cover the nature of the disease, transmission issues, and risk reduction.

Nature of the Disease

Chlamydia is commonly asymptomatic in both men and women and reinfection occurs commonly after treatment. In women, there is an increased risk of upper reproductive tract damage with reinfection. Accordingly, all persons with a diagnosis of urogenital chlamydial infection should have repeat testing for *C. trachomatis* 3 months after treatment.

Transmission Issues

Patients and their sex partners should abstain from sexual intercourse until they and their sex partners have completed treatment. Abstinence should be continued until 7 days after a single-dose regimen or after completion of a 7-day regimen. Timely treatment of sex partners is essential for decreasing the risk for reinfecting the patient and for reducing the risk for complications. Effective treatment of chlamydia may impact HIV transmission and susceptibility.

Clinician Plan for Risk Reduction

The following are recommended for inclusion in a clinician's plan to help patients reduce their risk of acquisition and transmission of chlamydial infection.

- Assess the patient's behavior-change potential
- Develop individualized risk-reduction plans with the patient, and
- Discuss prevention strategies such as abstinence, monogamy with an uninfected partner, condoms, and limiting the number of sex partners. Latex condoms, when used consistently and correctly, can reduce the risk of transmission of chlamydia.
Summary Points

- Chlamydia is the most common reportable bacterial sexually transmitted infection in the United States, with more than 1.5 million cases reported in 2015 and peak incidence in females aged 15 to 24.
- *C. trachomatis* causes a wide range of clinical manifestations, including cervicitis, urethritis, pelvic inflammatory disease, infertility, pelvic pain, and perihepatitis in women, and urethritis and epididymitis in men. Other manifestations in men and women may include conjunctivitis, oropharyngeal infection, proctitis/proctocolitis, and reactive arthritis.
- Infants born to mothers with untreated *C. trachomatis* infection may develop conjunctivitis, trachoma, pneumonia, and urogenital infection.
- Screening for chlamydia in asymptomatic persons significantly reduces the incidence of chlamydia-associated complications and is recommended in all sexually active women younger than age 25, as well as in other persons at high risk of infection.
- In most circumstances, the preferred diagnostic method for chlamydial infection is with a *C. trachomatis* nucleic acid amplification test (NAAT), which is FDA-approved for chlamydia testing on (a) male and female urine samples, (b) clinician-collected endocervical, vaginal, and male urethral samples, and (c) self-collected vaginal swabs if obtained in a clinical setting.
- Standard treatment for genital chlamydial infections in non-pregnant women and men is with single-dose azithromycin or a 7-day course of twice-daily doxycycline.
- Persons who are diagnosed with chlamydia should receive counseling about the nature of infection, transmission, and risk reduction, and their sex partners should be referred for treatment; expedited partner therapy should be considered where permitted.
Citations


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Figures

Figure 1 Chlamydia trachomatis: Reported Cases in U.S., 1984-2015

As shown, the number of reported cases of chlamydia in the United States has steadily increased from 1984 to 2015.

Figure 2 Chlamydia—Rate, by Sex, 2000-2015

NOTE: Data collection for chlamydia began in 1984 and chlamydia was made nationally notifiable in 1995; however, chlamydia was not reportable in all 50 states and the District of Columbia until 2000.

Figure 3 Chlamydia—Rates of Reported Cases by Age Group and Sex, U.S. 2015

Figure 4 Chlamydia—Rates of Reported Cases by Race/Ethnicity, U.S. 2011-2015


Figure 5 Chlamydia—Rates of Reported Cases by Region, 2006-2015

Figure 6 Chlamydia—Rates of Reported Cases by State, 2015

NOTE: The total rate of reported cases of chlamydia for the United States and outlying areas (Guam, Puerto Rico, and Virgin Islands) was 475.3 cases per 100,000 population.

Figure 7 Chlamydia Prevalence among Sexually Active Females Aged 14-24, by Race/Ethnicity, 2007-2012

This graph shows the prevalence of chlamydia infection among sexually active females aged 14-24. NHANES = National Health and Nutrition Examination Survey

Figure 8 Life Cycle of Chlamydia

The elementary body attaches to and enters a host cell. The contact with the host cell membrane causes the elementary body to induce its own endocytosis. Within eight hours, the now-intracellular elementary body interacts with glycogen and transforms into a reticulate body, which begins to multiply within an isolated intracellular structure referred to as an inclusion. Within 48 hours, some of the reticulate bodies begin to reorganize back to elementary bodies. Within 72 hours, most of the reticulate bodies have transitioned back to elementary bodies and the inclusion either undergoes lysis at the host cell wall or the intact inclusion is released into the extracellular space. The elementary bodies are released to infect adjacent cells or to be transmitted to and infect another person.

Illustration by Jared Travnicek and David Ehlert, Cognition Studio
Figure 9 Reiters Syndrome and Circinate Balanitis

Source: photograph from Public Health—Seattle & King County STD Clinic.
Table 1. 2015 STD Treatment Guidelines: Chlamydial Infections
Treatment of Urogenital Chlamydial Infections in Adolescents and Adults

**Recommended for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults**

**Azithromycin**
1 g orally in a single dose

**Recommended for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults**

**Doxycycline**
100 mg orally twice a day for 7 days

**Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults**

**Erythromycin base**
500 mg orally four times a day for 7 days

**Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults**

**Erythromycin ethylsuccinate**
800 mg orally four times a day for 7 days

**Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults**

**Levofloxacin**
500 mg orally once daily for 7 days

**Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults**

**Ofloxacin**
300 mg orally twice a day for 7 days

### Table 2. 2015 STD Treatment Guidelines: Chlamydial Infections

#### Treatment of Chlamydial Infections During Pregnancy

**Recommended for Treatment of Chlamydial Infections During Pregnancy**

**Azithromycin**

1 g orally in a single dose

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**Alternative for Treatment of Chlamydial Infections During Pregnancy**

**Amoxicillin**

500 mg orally three times a day for 7 days

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**Erythromycin base**

500 mg orally four times a day for 7 days

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**Erythromycin base**

250 mg orally four times a day for 14 days

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**Erythromycin ethylsuccinate**

800 mg orally four times a day for 7 days

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**Erythromycin ethylsuccinate**

400 mg orally four times a day for 14 days

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**Source:** Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted...
Table 3. 2015 STD Treatment Guidelines: Chlamydial Infections
Treatment of Ophthalmia Neonatorum

*An association between oral erythromycin and azithromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants aged <6 weeks. Infants treated with either of these antimicrobials should be followed for signs and symptoms of IHPS.

Recommended for Treatment of Ophthalmia Neonatorum
Erythromycin base
50 mg/kg/day orally
divided into 4 doses
daily for 14 days*

Recommended for Treatment of Ophthalmia Neonatorum
Erythromycin ethylsuccinate
50 mg/kg/day orally
divided into 4 doses
daily for 14 days*

Alternative for Treatment of Ophthalmia Neonatorum
Azithromycin oral suspension
20 mg/kg/day orally,
1 dose daily for 3 days*

Table 4. 2015 STD Treatment Guidelines: Chlamydial Infections
Treatment of *Chlamydia trachomatis* Infant Pneumonia

**Recommended for Treatment of Chlamydia trachomatis Infant Pneumonia**

**Erythromycin base**
50 mg/kg/day orally
divided into 4 doses
daily for 14 days

**Recommended for Treatment of Chlamydia trachomatis Infant Pneumonia**

**Erythromycin ethylsuccinate**
50 mg/kg/day orally
divided into 4 doses
daily for 14 days

**Alternative for Treatment of Chlamydia trachomatis Infant Pneumonia**

**Azithromycin**
20 mg/kg/day orally,
1 dose daily for 3 days

Table 5. 2015 STD Treatment Guidelines: Chlamydial Infections
Treatment of Chlamydial Infections Among Infants and Children

Recommended for Infants and Children Who Weigh <45 kg

Erythromycin

*base*

50 mg/kg/day orally
divided into 4 doses
daily for 14 days

Note: Data are limited on the effectiveness and optimal dose of azithromycin for the treatment of chlamydial infection in infants and children who weigh <45 kg

Recommended for Infants and Children Who Weigh <45 kg

Erythromycin

*ethylsuccinate*

50 mg/kg/day orally
divided into 4 doses
daily for 14 days

Note: Data are limited on the effectiveness and optimal dose of azithromycin for the treatment of chlamydial infection in infants and children who weigh <45 kg

Recommended

Recommended for Children Who Weigh ≥45 kg but Who Are Aged <8 Years

Azithromycin

1 g orally in a single
dose

Recommended

Recommended for Children Aged ≥8 years

Azithromycin

1 g orally in a single
dose

Recommended for Children Aged ≥8 years

Doxycycline

100 mg orally twice
da day for 7 days
