Chlamydia

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Module 1: Pathogen-Based Diseases
Lesson 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 1,808,703 reported cases in 2019.[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 1980s (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. Since 2015, there has been nearly a 20% increase in reported chlamydia cases in the United States. The following summarizes several key epidemiologic features of chlamydial infections as reported for 2019 in the United States.[1]

- **Sex**: Rates of reported chlamydial have consistently been higher in females than in males; in 2019, the rate in females (698.9) was 1.75 times higher than in males (399.9)(Figure 2).[1]
- **Age**: Among different age groups, the highest chlamydial rates (per 100,000 population) by far occur in persons 20 to 24 years of age, with the next highest among persons 15 to 19 years of age (Figure 3).[1]
- **Sex and Age Group**: Among females and males, the highest rates (reported cases per 100,000 population) occur among those 20 to 24 years of age, followed next by those 15 to 19 years of age for females and 25 to 29 years of age for males (Figure 4).[1]
- **Race/Ethnicity**: Rates of chlamydial infection are Racial and ethnic minorities are disproportionately higher among persons in certain racial and ethnic groups, with the highest rates among Black persons (Figure 5).[1] Factors that may contribute to these inequities include differential access to quality health care, social and economic conditions, higher prevalence of disease in sexual networks, and differences in immunogenetic determinants that influence the immune response to chlamydia.
- **Region and State**: The South has consistently had the highest rate of reported chlamydia cases, although the difference between the rate in the South and other regions is small (Figure 6).[1] The five states with the highest rates of reported chlamydia cases (in descending order) are Alaska, Louisiana, Mississippi, South Carolina, and New Mexico; of note, the rate of reported cases in Washington DC is markedly higher than any state (Figure 7).[1]

Prevalence

Based on data from the National Health and Nutrition Examination Surveys (NHANES), the CDC estimated an overall prevalence of 2.35 million chlamydial infections in the United States among persons 15 to 39 years of age in 2018, with approximately two-thirds of these infections in persons 15 to 24 years of age.[3]
Factors Associated with Acquisition of Chlamydia

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.[4] 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.[5] 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 nonviral STI and the most significant contributor to cost, with total lifetime direct medical costs estimated at $516.7 million.[4,6,7,8] 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.[9,10] In addition, studies have shown that rectal chlamydia infection in men who have sex with men significantly increases the risk of HIV acquisition.[11] Screening for rectal chlamydia in men who have sex with men can be a cost-effective intervention for HIV prevention.[12]
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.[13] 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. *Chlamydia 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

*Chlamydia 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.[14,15] The organisms replicate within a host cell, eventually causing death of the host cell.[16] 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 noninfectious replicating form.
3. Within 48 hours, some 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%.[17] 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 (OmpA serovar) or molecular methods (OmpA genotype).[18,19,20] Genital, rectal, oropharyngeal, and conjunctival infections are usually caused by *C. trachomatis* serovars D through K (as is conjunctivitis and pneumonia in neonates), chronic keratoconjunctivitis (trachoma) by serovars A-C, and lymphogranuloma venereum (LGV) by serovars L1-L3.[15,19] 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. *Chlamydia 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.[21] 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 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.[22] 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.[22]

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 women with chlamydia infection. 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 bleeding.[23,24] 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.[10,25] 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 of those who conceive, about 1% will have an ectopic pregnancy.[26] The extensive long-term morbidity associated with chlamydial infection underscores the importance of aggressive prevention, screening, and treatment programs.[4,27]

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.[28,29] 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.[30]

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 *C. trachomatis* most frequently is asymptomatic in both men and women.[31] 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.[32]

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.[33] 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. Chronic infection can rarely cause scarring and fistula formation. Lymphogranuloma venereum more often presents as proctitis or proctocolitis, and therefore additional diagnostic methods are required to differentiate LGV from non-LGV strains of *C. trachomatis*.[34,35]

**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.[34] 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).[2]

**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.[36] 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 younger 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.[37] 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.[38] 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.[2] 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.\[35\] 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)**

Nucleic acid amplification tests (NAATs) amplify nucleic acid sequences (either DNA or RNA) that are specific for the organism being detected. Similar to other nonculture tests, NAATs can detect live or non-viable organisms. Multiple commercially-available NAATs are FDA-cleared as diagnostic tests for *C. trachomatis* on urine specimens from men and women, urethral secretions in men, and endocervical swabs in women; some tests are cleared for vaginal swabs.[2] In addition, in May 2019 the FDA cleared two NAATs for diagnostic testing of chlamydia at extragenital sites (pharynx and rectum); the two tests are the Aptima Combo 2 Assay and the Xpert CT/NG.[39] For chlamydia testing in men, NAATs are highly sensitive for detecting *C. trachomatis* on either urethral secretions or a first-catch urine specimen, but most experts prefer using urine samples.[2] For 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.[40,41,42,43,44] In addition, in men and women, self-collected rectal swabs for NAAT have also performed well.[45]

**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 a significantly lower sensitivity (range 50% to 75%) than NAATs.[46] 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).[35] 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.[47] The more sensitive and species-specific MIF has replaced the CFT. High background prevalence and infrequent rises and falls in IgG and IgM make serology 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 extragenital 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, such as 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 Chlamydial Infection

Screening for chlamydia in asymptomatic persons has been found to significantly reduce the incidence of chlamydia-associated PID.[27,48,49] In general, routine screening for chlamydia should utilize NAAT as the diagnostic test; the United States FDA has cleared NAATs for chlamydia testing on (1) male and female urine samples, (2) male and female rectal and throat samples; (3) clinician-collected endocervical, vaginal, and male urethral samples, and (4) self-collected vaginal swabs if obtained in a clinical setting. The following summarizes recommendations in the 2015 STD Treatment Guidelines and the 2014 USPSTF for routine chlamydia screening; in addition, these recommendations incorporate the 2019 FDA clearance to use NAATs for extragenital (rectum and pharynx) diagnostic testing for \textit{C. trachomatis}.[2,4,39]

- **Women Who Have Sex with Men**: The high frequency of asymptomatic infection among young women combined with greater risk for morbidity led to the recommendation by the CDC and the USPSTF that all sexually active females younger than 25 years of age undergo annual screening for chlamydial infection.[2,4] More frequent screenings may be appropriate for sexually active adolescents and women with recent \textit{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 sex partner, more than one sex partner, a sex partner with concurrent (overlapping) partners, or a sex partner who has been diagnosed with an STI. Women diagnosed with chlamydia should have repeat testing approximately 3 months after completing treatment.

- **Women Who Have Sex with Women**: The CDC recommends that chlamydia screening for sexually active women who have sex with women should be based on the same recommendations as for sexually active women who have sex with men.[50]

- **Pregnancy**: At the first prenatal visit, screen all pregnant women younger than 25 and those older than 25 who have increased risk of acquiring chlamydial infection.[50] Identified factors associated with increased risk for chlamydial infection include a new sex partner, more than one sex partner, a sex partner with concurrent (overlapping) partners, or a sex partner who has been diagnosed with an STI. Retest for chlamydial infection during the third trimester in women younger than 25 and in women older than 25 who have increased risk of acquiring chlamydial infection. Pregnant women diagnosed with chlamydia should have a test-of-cure 3 to 4 weeks after completing treatment, and they should have repeat testing for chlamydia approximately 3 months after completing treatment.

- **Men Who Have Sex Only with Women**: Routine screening for chlamydial infection is not recommended by either the CDC or the USPSTF for sexually active men who have sex only with women.[2,4] The CDC recommends considering screening for chlamydia in sexually active young men who only have sex with women in populations with a high prevalence of chlamydia, including those seen at adolescent clinics, correctional facilities, and STD clinics.[2]

- **Men Who Have Sex with Men**: The CDC recommends routine chlamydia screening in sexually active men who have sex with men at least annually; the screening should consist of testing genital and rectal sites exposed during sexual activity, regardless of a history of condom use during sexual exposure.[50] Routine testing of oropharyngeal testing for chlamydia infection is not recommended. 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. The USPSTF does not recommend routine screening for chlamydia in men who have sex with men.[4]

- **Transgender Men and Transgender Women**: The CDC recommends that screening for chlamydia in transgender men and transgender women should be based on age, current anatomy, and sexual practices.[50]

- **Persons with HIV Infection**: The CDC recommends performing routine screening for chlamydia for persons with HIV infection who are sexually active; testing for chlamydia should be performed at the initial evaluation and at least annually thereafter (more frequent screening may be indicated based on risk).[51] The testing should consist of obtaining samples from the anatomic sites of sexual exposure, with the exception that routine screening for oropharyngeal chlamydia infection is not recommended.

- **Correctional Facilities**: The CDC recommends performing routine screening for chlamydial infection at the initial intake in a correctional facility for all women 35 year of age and younger and men younger than 30 years of age.[50]
Adolescents and Adults with Urogenital Chlamydia Infections

The 2015 STD Treatment Guidelines recommend treatment of urogenital chlamydial infections with either azithromycin 1 gram orally as a single dose or doxycycline 100 mg orally twice daily for seven days (Table 1). [2] Most studies show comparable efficacy between these two regimens. [52, 53] Azithromycin has the 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. [54, 55] 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. trachomatis strains. [2, 56] 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. trachomatis infection. [57, 58, 59, 60, 61]

Adults with Oropharyngeal Chlamydial Infections

The clinical significance of oropharyngeal C. trachomatis infection remains unclear and routine screening for oropharyngeal C. trachomatis infection is not recommended. Since oropharyngeal C. trachomatis can be transmitted to genital sites of sex partners, [62, 63], detection of C. trachomatis from an oropharyngeal sample warrants treatment with either azithromycin 1 gram orally as a single dose or doxycycline 100 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. This strategy has been demonstrated to decrease the rate of recurrent or persistent chlamydia infection. [64, 65, 66] Use of expedited partner therapy 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 expedited partner therapy 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 expedited partner therapy is contraindicated in a female partner who have current signs or symptoms that are suggestive of PID. Female partners who have current signs and symptoms suggestive of PID should undergo prompt evaluation by a health care provider. Finally, expedited partner therapy 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 expedited partner therapy in each state in the United States, 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]

**Posttreatment Follow-Up**

The CDC does not recommend routine test-of-cure after completing therapy for chlamydia in nonpregnant persons, but all females and males 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]

**Treatment of Chlamydial Infections During Pregnancy**

The recommended regimen for treatment of chlamydial infections in pregnant women is azithromycin 1 gram orally in a single dose.[2,67,68,69,70] 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 for the treatment of 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-of-cure performed 3 weeks after completion of therapy. Women younger than 25 years of age 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.[71,72] Thus, infants treated with erythromycin should be followed for signs and symptoms of infantile hypertrophic pyloric stenosis.[73] 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 of infantile hypertrophic pyloric stenosis, particularly if given in the first 2 weeks of life.[73,74]

**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 2015 STD Treatment 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: (1) 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 infants and children who weight less than 45 kg, the preferred treatment of chlamydial infections (other than ophthalmia neonatorum) is erythromycin base or erythromycin ethylsuccinate 50 mg/kg/day orally divided into 4 doses daily for 14 days.[2] For children younger than 8 years of age and weighing 45 kg or greater, the recommended regimen is azithromycin 1 gram orally in a single dose. Children older than 8 years of age should be treated with azithromycin 1 gram orally in a single dose or doxycycline 100 mg twice daily for 7 days. A follow-up visit with chlamydia culture is recommended approximately 2 weeks after completion of treatment to evaluate for treatment effectiveness.[2] Use of NAATs for the 2-week follow-up test is not appropriate due to false-positive results from residual C. trachomatis nucleic acids at 2 weeks post-treatment.[35]

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. This is imperative for sexually active females aged 14 through 24 years among whom chlamydia prevalence was 4.7% from 2007 through 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 could have an impact on reducing HIV transmission and acquisition.

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, condom use, 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 approximately 1.75 million cases reported in 2018.
- The peak incidence of chlamydia infections in the United States occurs in females aged 15 to 24 years.
- *Chlamydia 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* NAAT, which is FDA cleared for chlamydia testing on (1) male and female urine samples, (2) male and female rectal and throat samples, (3) clinician-collected endocervical, vaginal, and male urethral samples, and (4) self-collected vaginal swabs if obtained in a clinical setting.
- Standard treatment for genital chlamydial infections in nonpregnant females and all males 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


References


• Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. Atlanta: U.S. Department of Health and Human Services; October 2019. [CDC] -


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[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

• Lau A, Kong F, Fairley CK, et al. Treatment efficacy of azithromycin 1 g single dose versus doxycycline 100 mg twice daily for 7 days for the treatment of rectal chlamydia among men who have sex with men - a double-blind randomised controlled trial protocol. BMC Infect Dis. 2017;17:35. [PubMed Abstract] -


• Weinstock H, Berman S, Cates W Jr. Sexually transmitted diseases among American youth: incidence

Figures

Figure 1 *Chlamydia trachomatis*: Reported Cases in United States, 1984-2019

As shown, the number of reported cases of chlamydia in the United States has steadily increased from 1984 to 2019.

Figure 2 Chlamydia—Rate of Reported Cases, by Sex, United States, 2012-2019

The rate for cases of chlamydia was consistently higher in females than in males during 2012 to 2019.

Figure 3 Chlamydia—Rate of Reported Cases, by Age Group, United States, 2019

Figure 4 Chlamydia—Rates of Reported Cases by Sex and Age Group, United States, 2019


<table>
<thead>
<tr>
<th>Age Group</th>
<th>Male Rate*</th>
<th>Female Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-14</td>
<td>109.0</td>
<td>98.8</td>
</tr>
<tr>
<td>15-19</td>
<td>1,009.0</td>
<td>3,333.8</td>
</tr>
<tr>
<td>20-24</td>
<td>1,871.5</td>
<td>4,109.5</td>
</tr>
<tr>
<td>25-29</td>
<td>1,167.2</td>
<td>1,729.0</td>
</tr>
<tr>
<td>30-34</td>
<td>702.1</td>
<td>774.2</td>
</tr>
<tr>
<td>35-39</td>
<td>404.1</td>
<td>379.6</td>
</tr>
<tr>
<td>40-44</td>
<td>242.1</td>
<td>193.5</td>
</tr>
<tr>
<td>45-54</td>
<td>122.4</td>
<td>72.3</td>
</tr>
<tr>
<td>55-64</td>
<td>46.9</td>
<td>20.0</td>
</tr>
<tr>
<td>65+</td>
<td>8.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Total</td>
<td>399.9</td>
<td>698.9</td>
</tr>
</tbody>
</table>

*Per 100,000 population
Figure 5 Chlamydia—Rates of Reported Cases by Race/Ethnicity, United States, 2019

Figure 6 Chlamydia—Rates of Reported Cases by Region in United States, 2012-2019

Figure 7 Chlamydia—Rates of Reported Cases by State, 2019


*Rate = per 100,000 population.*
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 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 Reiter's 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

<table>
<thead>
<tr>
<th>Recommended for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
</tr>
<tr>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doxycycline</strong></td>
</tr>
<tr>
<td>100 mg orally twice a day for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythromycin base</strong></td>
</tr>
<tr>
<td>500 mg orally four times a day for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythromycin ethylsuccinate</strong></td>
</tr>
<tr>
<td>800 mg orally four times a day for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Levofloxacin</strong></td>
</tr>
<tr>
<td>500 mg orally once daily for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Urogenital Chlamydial Infections in Adolescents and Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ofloxacin</strong></td>
</tr>
<tr>
<td>300 mg orally twice a day for 7 days</td>
</tr>
</tbody>
</table>

# Table 2. 2015 STD Treatment Guidelines: Chlamydial Infections
## Treatment of Chlamydial Infections During Pregnancy

<table>
<thead>
<tr>
<th>Recommended for Treatment of Chlamydial Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
</tr>
<tr>
<td>1 g orally in a single dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Chlamydial Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin</strong></td>
</tr>
<tr>
<td>500 mg orally three times a day for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Chlamydial Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythromycin base</strong></td>
</tr>
<tr>
<td>500 mg orally four times a day for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Chlamydial Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythromycin base</strong></td>
</tr>
<tr>
<td>250 mg orally four times a day for 14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Chlamydial Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythromycin ethylsuccinate</strong></td>
</tr>
<tr>
<td>800 mg orally four times a day for 7 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Chlamydial Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythromycin ethylsuccinate</strong></td>
</tr>
<tr>
<td>400 mg orally four times a day for 14 days</td>
</tr>
</tbody>
</table>

### 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* |

**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

<table>
<thead>
<tr>
<th>Recommended for Treatment of Chlamydia trachomatis Infant Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin base</td>
</tr>
<tr>
<td>50 mg/kg/day orally divided into 4 doses daily for 14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommended for Treatment of Chlamydia trachomatis Infant Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin ethylsuccinate</td>
</tr>
<tr>
<td>50 mg/kg/day orally divided into 4 doses daily for 14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative for Treatment of Chlamydia trachomatis Infant Pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
</tr>
<tr>
<td>20 mg/kg/day orally, 1 dose daily for 3 days</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Weight</th>
<th>Treatment Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infants and Children Who Weigh &lt;45 kg</strong></td>
<td><strong>Erythromycin base</strong> 50 mg/kg/day orally divided into 4 doses daily for 14 days</td>
<td>Note: Data are limited on the effectiveness and optimal dose of azithromycin for the treatment of chlamydial infection in infants and children who weigh &lt;45 kg</td>
</tr>
<tr>
<td><strong>Infants and Children Who Weigh &lt;45 kg</strong></td>
<td><strong>Erythromycin ethylsuccinate</strong> 50 mg/kg/day orally divided into 4 doses daily for 14 days</td>
<td>Note: Data are limited on the effectiveness and optimal dose of azithromycin for the treatment of chlamydial infection in infants and children who weigh &lt;45 kg</td>
</tr>
<tr>
<td><strong>Children Who Weigh ≥45 kg but Who Are Aged &lt;8 Years</strong></td>
<td><strong>Azithromycin</strong> 1 g orally in a single dose</td>
<td></td>
</tr>
<tr>
<td><strong>Children Aged ≥8 years</strong></td>
<td><strong>Azithromycin</strong> 1 g orally in a single dose</td>
<td></td>
</tr>
<tr>
<td><strong>Children Aged ≥8 years</strong></td>
<td><strong>Doxycycline</strong> 100 mg orally twice a day for 7 days</td>
<td></td>
</tr>
</tbody>
</table>
