Sexually Transmitted Chlamydial Infections

A Primary Care Clinician's Guide to Diagnosis, Treatment and Prevention

California Chlamydia Action Coalition

California STD/HIV Prevention Training Center

A Continuing Medical Education Program
Sponsored by
The California STD/HIV Prevention Training Center
& The California Chlamydia Action Coalition

The purpose of this educational activity is to increase the skills of primary care clinicians in the recognition and treatment of sexually transmitted chlamydial infection.

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To order additional copies of this booklet, contact Pitney Bowes at (415) 356-7681.

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Learning Objectives

Upon completion of this education program, the clinician should be able to:

- Describe the biology and pathogenesis of *Chlamydia trachomatis.*
- Define the epidemiology and risk factors for sexually transmitted chlamydial infections.
- List the clinical manifestations of chlamydial infections in women and men.
- Describe the different laboratory methods available for the diagnosis of chlamydial infections, their sensitivity and specificity, advantages and disadvantages.
- Discuss appropriate chlamydia screening strategies to identify early infection and prevent complications and recurrent infections.
- List the recommended antibiotic treatment for uncomplicated chlamydial infections in women and men, and describe their indications and contraindications.
- Describe the case management of patients infected with chlamydia and their sexual partners, including counseling and follow-up testing of patients and notification, testing, and treatment of partners.

Abbreviations

CDC	Centers for Disease Control and Prevention
CMT	Cervical Motion Tenderness
DFA	Direct Fluorescent Antibody
DNA	Deoxyribonucleic Acid
EB	Elementary Body
EES	Erythromycin Ethylsuccinate
EIA	Enzyme Immunoassay
GNDC	Gram-negative Diplococci
FDA	Food and Drug Administration
HEDIS	Health Plan Employer Data and Information Set
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IgG	Immunoglobulin G
IgM	Immunoglobulin M
LCR	Ligase Chain Reaction
LGV	Lymphogranuloma Venereum
MPC	Mucopurulent Cervicitis
NAAT	Nucleic Acid Amplification Test
NGU	Non-Gonococcal Urethritis
PCR	Polymerase Chain Reaction
PID	Pelvic Inflammatory Disease
PMN	Polymorphonuclear Leukocytes
RB	Reticulate Body
RNA	Ribonucleic Acid
SDA	Strand Displacement Amplification
STD	Sexually Transmitted Disease
TMA	Transcription Mediated Amplification

Introduction

Chlamydia trachomatis is the most commonly reported notifiable disease in the U.S.[1] The infection in women, which is asymptomatic in 70-90% of cases, can lead to pelvic inflammatory disease (PID), chronic pelvic pain, ectopic pregnancy, and infertility.[2] Although the majority of infected men are also asymptomatic, chlamydia is an important cause of acute non-gonococcal urethritis, proctitis, and epididymitis, and has been linked to Reiter's syndrome.[2] Chlamydia also plays an important role in increasing the susceptibility to and transmission of HIV infection.[3] Perinatal transmission to neonates can cause conjunctivitis and pneumonia.[4]

Because chlamydial infections are generally asymptomatic, they are often undetected until costly medical sequelae have developed. Consequently, costs associated with chlamydia exceed $2 billion annually.[5] However, routine screening and early identification of persons at high risk of sexually transmitted infection can prevent many long term complications.

Biology & Pathogenesis

Chlamydia trachomatis is a member of the Chlamydiaceae family. It is an obligate intracellular bacterium, has DNA and RNA, bacterial ribosomes, and a cell wall similar to Gram-negative organisms.[6] The genus

BIOLOGY KEY POINTS:

- Obligate intracellular bacteria
- C. trachomatis species with several serovars associated with distinct clinical syndromes
- Intracellular and extracellular forms
- Growth cycle takes 48-72 hours
- Infects columnar squamous epithelium of the urogenital tract, rectum, and conjunctiva

Chlamydia contains 3 species that infect humans: *C. pneumoniae, C. psittaci, and C. trachomatis*. Both *C. pneumoniae* and *psittaci* are well known causes of pneumonia. *C. trachomatis* causes several distinct clinical syndromes in humans including trachoma, urogenital infections, conjunctivitis, neonatal pneumonia, and lymphogranuloma venereum (LGV).

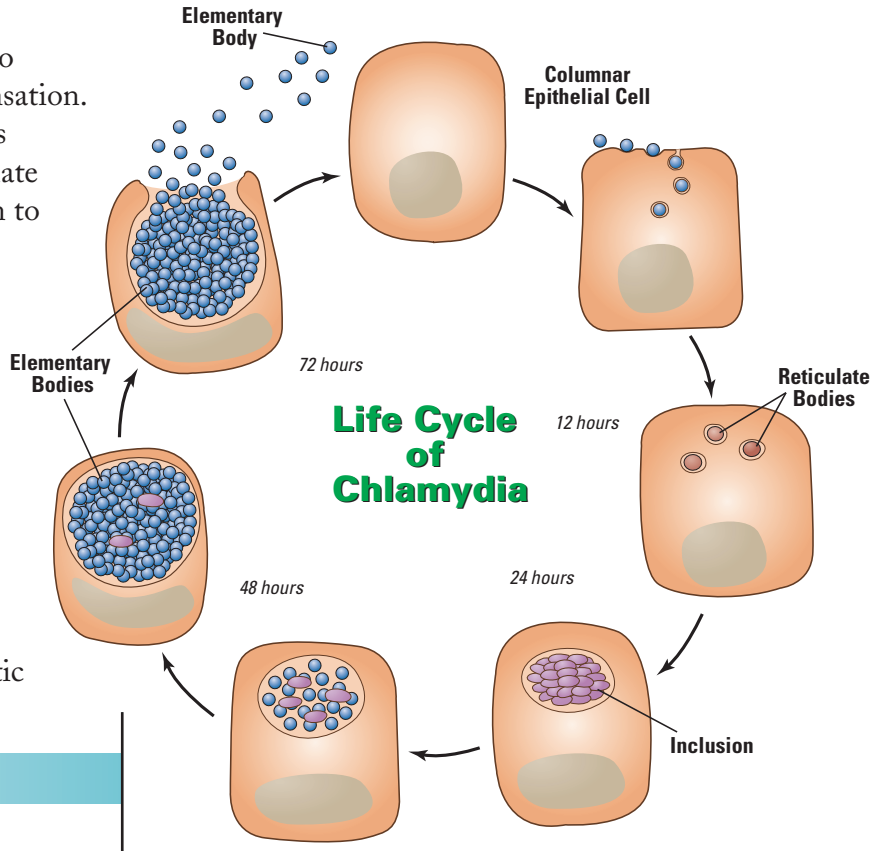
The *Chlamydiae* have a complex life cycle that involves two forms of the organism: the elementary body (EB), which is the non-replicating extracellular infective form, and the reticulate body (RB), which is the intracellular replicative form. The life cycle begins when an elementary body adheres to and is endocytosed into a host transitional or columnar epithelial cell. Once inside the host cell, the elementary body transforms into a reticulate body. In the growth phase, the reticulate bodies undergo binary fission within vacuoles called inclusions.

CLASSIFICATION OF CHLAMYDIA SPECIES

Species	Serovar	Clinical Syndrome
C. *trachomatis*	A, B, Ba, C	Trachoma
	D → K	Urogenital, rectal, conjunctival infections
		Neonatal pneumonia
	L_1, L_2, L_3	Lymphogranuloma venereum (LGV)
C. *pneumoniae*		Pharyngitis, bronchitis, pneumonia
C. *psittaci*		Psittacosis

The reticulate bodies then reorganize into elementary bodies through DNA condensation. After 48-72 hours, the elementary bodies are released from the infected cell to initiate infection of adjacent cells or transmission to another person.

C. trachomatis infects the superficial mucosa (squamocolumnar and columnar epithelial cells) of the urinary tract, reproductive tract, conjunctiva, gastrointestinal tract, and respiratory tract. It is now believed that part of the tissue damage caused by chlamydial infections is due to an immunologic or hypersensitivity mechanism. Despite this, the majority of infections are asymptomatic and may persist for months to years.[7]



Epidemiology

Incidence in the U.S.

Each year, an estimated 3-5 million cases of sexually transmitted chlamydial infection occur in the U.S. with the highest infection rates seen in women under age 25. In 2000, over 700,000 cases were reported to the CDC, for a rate of 257.5 cases per 100,000 persons.[8] This was nearly double the number of gonorrhea cases reported. Reported rates of chlamydia increased dramatically in the U.S. during the 1990s, in part due to increased screening, expanded reporting requirements, and improved diagnostic technology. Chlamydial infections have a wide geographic and socioeconomic distribution. Nearly every state in the country has a rate over 150 cases per 100,000 population.

Prevalence in the U.S.

The prevalence of chlamydial infections varies according to the clinic setting, age, and gender.[9] Among young women, high positivity rates are seen in public STD clinics (10-30%), juvenile corrections (15-30%), school-based clinics (10-15%), family planning clinics (5-10%), managed care organizations (5-10%), and prenatal clinics (5-10%).[10, 11] Among men, high positivity rates are seen in STD clinics (10-20%), juvenile corrections (5-9%), and military recruits (4%).[12, 13]

Risk Factors

Young age and female gender are the most important risk factors for chlamydial infection. Additional risk factors identified for chlamydial infection include new or multiple sex partners, inconsistent use of barrier contraceptives, use of oral contraceptives, cervical ectopy, douching, and black race and low socioeconomic status.[14-16]

Transmission

Chlamydial infection is highly transmissible, with 65-70% of exposed sex partners concurrently infected.[17] Initially, transmission was thought to be more efficient from an infected man to his female partner, however, recent studies have demonstrated that transmission rates may be similar between

genders. Based on very limited data, orogenital contact seems inefficient for transmission of chlamydial infections, although well-designed transmission studies are difficult to conduct for ethical reasons.

EPIDEMIOLOGY KEY POINTS:

- Chlamydia is the most common reportable STD in the U.S.
- Chlamydia is widespread throughout the U.S.
- Adolescent and young women are at the highest risk of infections
- Risk factors include new or multiple partners and inconsistent use of condoms

Clinical Manifestations

Infections with *C. trachomatis* produce urogenital disease, neonatal infection, conjunctivitis, and lymphogranuloma venereum. Sexually transmitted infection is by far the most common manifestation of disease in the U.S. and is responsible for the vast majority of the burden of disease and economic costs due to chlamydial infections. Because the majority of chlamydial infections are asymptomatic, early identification in women through annual screening and treatment reduces the incidence of long-term complications.

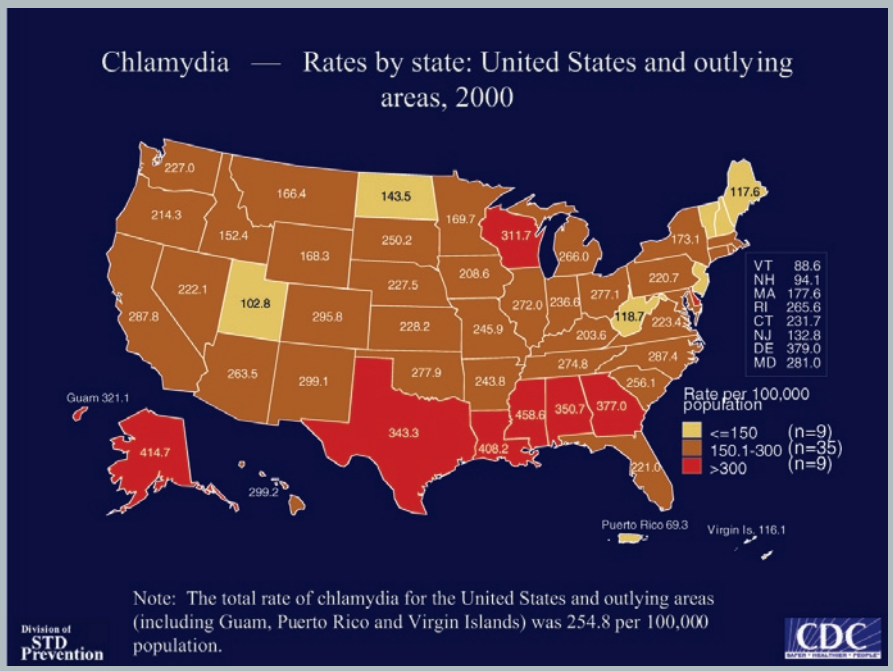
Urogenital Infections In Women

In the minority of women with chlamydia who have clinical findings, the spectrum of urogenital disease in women includes, but is not limited to, cervicitis, urethritis, bartholinitis, pelvic inflammatory disease (PID), and perihepatitis.[2] Symptomatic women may complain of vaginal discharge, abnormal vaginal bleeding, abdominal or pelvic pain, dysuria, or dyspareunia. The pelvic exam may be normal or reveal cervicitis, cervical motion tenderness (CMT), or uterine or adnexal tenderness.

Cervicitis

Among women with urogenital chlamydial infection, the cervix is the most common site of infection (75-80%). Although the majority of women with cervical chlamydial infection are asymptomatic, up to 30% have evidence of mucopurulent cervicitis (MPC) on speculum exam. MPC is characterized by a purulent or mucopurulent exudate visible in the endocervix or on an endocervical swab (positive swab

Chlamydia in the United States



Source: Division of STD Prevention. Sexually Transmitted Disease Surveillance, 2000. USDHHS, PHS. Atlanta: Centers for Disease Control and Prevention, 2001.

Disease in Women

- Cervicitis
- Urethritis
- Bartholinitis
- PID
- Perihepatitis
- Proctitis
- Conjunctivitis
- LGV
- Reiter's Syndrome

Disease in Men

- Urethritis (NGU)
- Epididymitis
- Proctitis
- Conjunctivitis
- LGV
- Reiter's Syndrome

test). Cervical friability (spontaneous or easily induced endocervical bleeding of the cervix) is also a sign of MPC. An increased number of white cells on a Gram stain of cervical discharge or exudate is no longer considered a criterion for diagnosis, as it has poor predictive value and has not been standardized.

Urethritis

Some patients may present with an acute urethral syndrome or urethritis characterized by dysuria and demonstration of fewer than 10^5 bacteria/ml of urine. Among women with urogenital infection, the urethra is a frequent site of infection (50-60%).

Pelvic Inflammatory Disease (PID)

An estimated 1 million women develop PID every year in the U.S. PID is the leading cause of preventable infertility in the U.S. Up to 40% of women with untreated chlamydial infection will develop PID.[18] Due to tubal scarring, 20% of these women will progress to develop infertility, 18% will develop chronic pelvic pain, and 6% will have an ectopic pregnancy. The risk of infertility doubles with each episode of PID.[19, 20]

Although various organisms have been associated with the development of PID, chlamydia has been demonstrated to infect the fallopian tubes or endometrium in over half of cases. The infection generally begins in the lower genital tract and ascends to the fallopian tubes to produce salpingitis. Infection in the tubes can also lead to tubo-ovarian abscess, which carries a risk of rupture and bleeding. The time required for spread from cervix to upper tract is still unclear. Lower abdominal pain, cervical motion tenderness, and adnexal or uterine tenderness in a sexually active woman suggest a diagnosis of PID. Chlamydia also causes "silent PID", inflammation without symptoms, that is associated with increased risk for infertility and ectopic pregnancy. Treatment for PID includes antibiotic regimens that provide empiric coverage for chlamydia, gonorrhea, anaerobes, and other likely pathogens.[21]

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Perihepatitis (Fitz-Hugh-Curtis Syndrome)

This rare syndrome is characterized by right upper quadrant pain, nausea, vomiting, fever, and normal transaminases. About 70% of perihepatitis cases are associated with chlamydia. PID may not be clinically evident. Although thought to be caused by direct spread of the organism from the infected fallopian tubes to the capsule of the liver, hematogenous and lymphatic spread may also occur. Inflammation of the liver capsule may lead to intra-abdominal adhesions.

Urogenital Infections In Men

Over 50% of urogenital chlamydial infections in men are asymptomatic. When symptoms are present, nongonococcal urethritis (NGU) is the most common manifestation of chlamydial infection. Other manifestations of disease in men include epididymitis, proctitis, and Reiter's syndrome.[2] Chlamydial infections among men readily respond to treatment with antibiotics and rarely produce long-term medical sequelae.

Urethritis (Non-Gonococcal Urethritis)

Symptomatic men with NGU typically present with mucoid urethral discharge and dysuria. Symptoms of NGU are often mild and develop slowly over a few days. The incubation period is estimated to be 5-10 days, but may be longer. NGU in men is defined on the Gram stain of a urethral specimen by the presence of at least 5 PMNs per oil immersion field (1000x) in the absence of intracellular Gram-negative diplococci (GNDC). Chlamydial organisms are not visualized on Gram stain. If Gram stain is unavailable, the diagnosis of urethritis can be supported by a positive leukocyte esterase test or the presence of at least 10 PMNs per high power field (400x) on first-void urine.

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Epididymitis

Sexually transmitted epididymitis is most commonly seen in men less than 35 years of age, and 70% of cases are attributable to chlamydia. *Neisseria gonorrhoeae* also can cause epididymitis. Epididymitis can be caused by non-STD pathogens, mainly *E. coli* and *Pseudomonas*. These infections occur more commonly in men over the age of 35 and in men who engage in insertive anal intercourse. Overall, it is an uncommon complication, occurring in less than 2% of men with urogenital chlamydial infections.

Patients typically present with unilateral scrotal pain, fever, and epididymal tenderness or swelling. Clinical examination findings include epididymal or testicular tenderness, swelling, and mass. Urethritis may be a clinical feature of the disease. The similarity in presentation to testicular torsion warrants consideration of diagnostic studies to rule out this urologic emergency. In correlation with exam findings, confirmed NGU is presumptive of chlamydial epididymitis. A positive test for chlamydia from the urethra or the epididymal aspirate is diagnostic. Empiric treatment for epididymitis provides coverage for chlamydia, gonorrhea and other potential pathogens.[21]

Anorectal Infection (Proctitis)

Proctitis is seen almost exclusively in homosexual men engaging in receptive anal intercourse; however, women also are susceptible. Rectal infections are generally asymptomatic but may cause symptoms characteristic of proctitis.[2]

Proctitis is manifested by rectal discharge, bleeding, tenesmus, and pain during defecation. If caused by non-LGV strains, proctitis is usually mild. Anoscopy reveals patchy mucosal friability and mucopurulent discharge in the distal rectum. A rectal Gram stain with at least 1 PMN without intracellular GNDC is presumptive of chlamydial proctitis, and a positive test for chlamydia is diagnostic.

Conjunctivitis

Ocular or ophthalmic infections may result from exposure to infectious genital secretions during sexual contact or by autoinoculation. Ocular disease usually presents as unilateral eye discomfort and hyperemia, with or without mucopurulent discharge. The conjunctiva often has a follicular appearance. Pre-auricular lymphadenopathy and otitis media may develop. Only 1% of persons with proven genital infection have ocular manifestations of infection while over 50% of persons with ocular infection have concurrent genital infection.[22] Treatment with the same recommended oral regimens as for genital infections is required.

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Lymphogranuloma Venereum

Lymphogranuloma venereum (LGV) is a sexually transmitted infection that is caused by *C. trachomatis* serovars L_1, L_2, and L_3. Disease usually presents as painful inguinal adenopathy up to 6 weeks after exposure to infection. In two-thirds of cases, the adenopathy is unilateral and may progress to become fluctuant and suppurative. Constitutional symptoms such as fever, chills, meningismus, myalgias or arthralgias also may be present. This syndrome presents most commonly in persons ages 20-30 years, and the highest prevalence of disease remains in Africa, Asia, and South America. Fewer than 200 cases per year were reported in the U.S. in the last several years.[23]

LGV serovars are also associated with proctocolitis. Signs and symptoms include severe rectal pain, discharge, hematochezia, fever, and lymphadenopathy. Anoscopy is markedly abnormal with lesions extending

into the colon. If untreated, this form of proctocolitis may lead to bowel obstruction. Treatment of LGV consists of a 3-week course of doxycycline.[21]

Reiter's Syndrome

Reiter's syndrome is a post-inflammatory autoimmune disease that occurs almost exclusively in men. Over 80% of persons with Reiter's syndrome are positive for the HLA-B27 phenotype. Other organisms, such as *Shigella, Salmonella, Yersinia*, and *Campylobacter* also have been associated with Reiter's syndrome, however, chlamydia accounts for up to 70% of cases with non-diarrheal disease.[24]

The disease occurs 3-6 weeks after a urogenital infection. The classic presentation involves conjunctivitis, urethritis, arthritis, and mucocutaneous skin lesions. Less common manifestations include keratoderma blenorrhagica and circinate balanitis. Most cases resolve completely within 2-6 months, but may last more than a year. Fifteen percent of cases will develop disease recurrence. Among men with NGU, 1-3% will develop Reiter's syndrome. Symptoms generally respond to non-steroidal anti-inflammatory agents.

Neonatal Infections

Nearly two-thirds of neonates born to infected mothers will develop chlamydial colonization after delivery. *C. trachomatis* can cause conjunctivitis and pneumonia in infants.[4] Approximately 18-50% of colonized newborns will develop conjunctivitis, and 11-20% will develop pneumonia. Exposed infants can also develop asymptomatic infections of the oropharynx, genital tract, and rectum. Detecting maternal chlamydial infection through routine prenatal screening and adequately treating before delivery prevents neonatal infections.

Inclusion Conjunctivitis

C. trachomatis is the most common cause of neonatal conjunctivitis in the U.S. Neonatal chlamydial conjunctivitis appears 5-14 days after birth and is characterized by hyperemia and mucopurulent discharge. Laboratory confirmation of *C. trachomatis* is required to differentiate the organism from other potential pathogens. Conjunctival cells (not just exudate) should be present on specimens being tested. Culture and non-culture tests can be used.

Ocular prophylaxis does not prevent infection to the newborn. Furthermore, prophylaxis aimed at the eye will fail to prevent direct infections or colonization by chlamydia at other sites, such as the vagina, rectum, oropharynx, nasopharynx, and lung.

Pneumonia

C. trachomatis is the etiologic agent in up to 20% of cases of infant pneumonia. Subacute, afebrile pneumonia due to chlamydia generally develops at age 1-3 months, and is characterized by a repetitive staccato cough with tachypnea, hyperinflation, and bilateral diffuse infiltrates on a chest x-ray. Wheezing is rare and peripheral eosinophilia is sometimes observed. Fifty percent of newborns will have a history of

CLINICAL KEY POINTS:

- Asymptomatic infection is common in both men and women
- Cervicitis is characterized by mucopurulent endocervical discharge and friability
- PID complications include ectopic pregnancy, chronic pelvic pain, and infertility
- Men may develop NGU that infrequently results in complications
- Neonatal infections may lead to conjunctivitis and pneumonia

conjunctivitis at the time of diagnosis. Untreated newborns may develop a protracted course of illness that may include apneic spells, asthma or obstructive airway disease. Although culture of nasopharyngeal specimens can be used to detect chlamydia, the presence of the organism in the nasopharynx is not diagnostic for pneumonia. High IgM titers are the best indicators of chlamydial pneumonia.

Laboratory Diagnosis

Laboratory confirmation of infection should be conducted for all patients suspected to have chlamydial infection. The diagnostic methods to detect chlamydial infection have changed significantly in the past few years. Currently available methods include tissue culture, detection of antigens using direct fluorescent antibody (DFA) or enzyme immunoassay (EIA), and detection of nucleic acid sequences by probe hybridization, enzymatic amplification, and hybrid capture.[25]

Because chlamydia is an intracellular bacterium, specimen collection has focused on obtaining columnar epithelial cells from the affected sites such as the endocervix or the urethra. Newer nucleic acid amplification technologies can detect even small fragments of chlamydial nucleic acid in urine or in vaginal swabs. Of note, blood in the specimen may interfere with test performance.

Tissue Culture

Tissue culture has been the gold standard diagnostic test because of its superior test performance characteristics compared with antigen detection and nucleic acid probe hybridization technologies. However, this status is being challenged because of its low sensitivity compared with new amplification technologies. The sensitivity of cell culture is variable (75-85%) but the specificity is nearly 100%. Because of the high specificity, culture is still recommended as the detection method for suspected cases of child sexual abuse. Culture can be used for all anatomical sites.

Tissue culture is labor and time intensive, and the successful recovery of organisms using this method requires strict attention to rigorous specimen handling and transport procedures. Swabs with wooden shafts should be avoided, as they can be toxic to chlamydia.

Periodic proficiency testing in laboratories is necessary to ensure specimens are processed according to recommended procedures. In addition, quality assurance testing should be performed to assess the adequacy of collection of the appropriate cell types for testing (i.e., columnar cells from the endocervix, urethra, rectum, or conjunctiva).[25]

Antigen Detection Methods

Both direct fluorescent antibody (DFA) and enzyme immunoassay (EIA) have been used for antigen detection. These tests detect organisms by immunologic methods and do not require live organisms. They are not approved for all anatomical sites.

Although the sensitivity and specificity of DFA (e.g., *MicroTrak*®) is dependent upon proper interpretation by a skilled microscopist, the test

Chlamydia Tests

- Tissue Culture
- Antigen Detection
  - EIA
  - DFA
- Nucleic Acid Detection
  - Probe Hybribization
  - Nucleic Acid Amplification (NAATs)
  - Hybrid Capture
- Serology

has a sensitivity of 70%-75% and a reported specificity of 95-99%. DFA is the only method where specimen adequacy can be evaluated as part of reading the test result because the presence of columnar cells can be determined while reviewing the slide for evidence of chlamydia.

EIA (e.g., Syva EIA), has a sensitivity of 50-75% and a specificity of 95-99%. This sensitivity makes EIA unsatisfactory for screening asymptomatic populations. To elicit better test performance characteristics from EIA technologies, confirmatory testing, verification assays, negative gray zone testing, and periodic quality assurance for specimen adequacy should be performed.[25, 26]

Non-Amplified Probe Hybridization

Non-amplified nucleic acid probe tests (Gen-Probe *PACE 2*®) are commonly used because of the ease of automation and reduced expense. Furthermore, this test offers the advantage of being able to detect both *C. trachomatis*

Comparison of Chlamydia Testing Technologies

	NUCLEIC ACID AMPLIFICATION TECHNOLOGY (NAAT)[a]	CELL CULTURE	DIRECT FLUORESCENT ANTIBODY (DFA)	ENZYME IMMUNO-ASSAY (EIA)	NUCLEIC ACID PROBE
Test Type	• Ligase Chain Reaction (LCR) • Polymerase Chain Reaction (PCR) • Transcription Mediated Amplification (TMA) • Strand Displacement Amplification (SDA)				
Collection Site	Male and female urine, endocervical and male urethral swabs	Endocervical, urethral, rectal, pharyngeal, conjunctival, pulmonary	Endocervical, male urethral, rectal, conjunctival, nasopharyngeal	Endocervical, male urethral, conjunctival, urine (symptomatic male)	Endocervical, male urethral, conjunctival
Sensitivity	90-95% [b]	75-85%	70-75%	50-75%	65-75%
Specificity	98-100%	100%	95-99%	95-99%	95-99%
Test Advantages	More sensitive. Non-invasive urine specimens in addition to genital swabs. Single specimen for chlamydia and gonorrhea.[c]	Recommended test for medicolegal purposes, if available.	Internally controlled for specimen adequacy. Refrigeration during transport not required.	Automated test. Refrigeration during transport not required.	Semi-automated. One swab for both chlamydia and gonorrhea. Refrigeration during transport not required.
Test Disadvantages	Contamination possible if specimen not handled properly in the clinic or lab. More costly.	Less sensitive. Longer turn around time. Technically difficult. Transport, storage and temperatures critical. Labor intensive. QA for specimen adequacy required.	Less sensitive. Technically difficult. Labor intensive.	Poor sensitivity. QA for specimen adequacy required. Confirmatory testing recommended.	Less sensitive. QA for specimen adequacy required. Confirmatory testing recommended. Negative gray zone testing recommended.

a Examples of current nucleic acid amplification tests are provided; others are under development.
b Sensitivity somewhat lower for urine compared to cervical swab specimens in nucleic acid amplification technology.
c Not all NAATs have complete clearance for gonorrhea testing of urine, particularly for asymptomatic patients.
Adapted from: USPHS Region IX Infertility Prevention Project. Clinical Guidelines. San Francisco, CA: Region IX Infertility Prevention Project Advisory Committee, 1998.

DIAGNOSIS KEY POINTS:

- Nucleic acid amplification tests (NAATs) are the most sensitive laboratory methods for detection of *C. trachomatis*
- Urine specimens can be used with new NAATs
- Tissue culture is recommended for medicolegal purposes
- Antigen-detection and non-amplified nucleic acid tests require supplemental testing to maximize performance
- Currently available rapid in-office tests are insensitive and not recommended

and *Neisseria gonorrhoeae* from the same swab specimen.

To elicit best test performance characteristics from nucleic acid probe hybridization technologies, confirmatory testing, verification assays, negative gray zone testing, and periodic quality assurance for specimen adequacy should be performed.[25, 26]

Nucleic Acid Amplification Tests

Nucleic acid amplification tests (NAATs) provide excellent sensitivity (90-95%) and specificity (98-100%). The amplification tests currently on the market are *LCx*® (Abbott, LCR), *Amplicor*® and *COBAS*® (Roche, PCR), *AmpCT*® and *APTIMA*® (Gen-Probe, TMA), and *ProbeTec*® (Becton-Dickinson, SDA). These tests identify up to 30% of chlamydial infections that would be missed by other methods.[27]

These tests offer the option of detecting *Neisseria gonorrhoeae* from the same specimen, however, not all NAATs have complete FDA clearance for gonorrhea testing on all collection sites. Further, the increase in sensitivity has enabled the use of noninvasive specimen collection, such as first-voided urine. These non-invasive methods eliminate the need for painful urethral swabs in men and pelvic examinations in women, particularly adolescents, thus, significantly increasing patient acceptability.[28] For these reasons, urine specimens are the test of choice for testing male patients and for screening women in settings where a pelvic exam is not indicated. Amplification tests have not been FDA-approved for pharyngeal and rectal specimens.

Contamination at the time of collection (i.e., the clinic site) or at the laboratory may result in false positive results. Because the amplification process is enzyme-dependent, the presence of inhibitors (e.g., blood) may cause false negative results; however, some assays have internal controls and methods of minimizing inhibition. Amplified tests cost more than nucleic acid probe and other tests.

Signal Amplification

The Digene *Hybrid Capture 2*® uses a signal-amplified nucleic acid hybridization assay to identify chlamydial infections. This test has a sensitivity somewhat less than NAATs and offers the option of detecting *C. trachomatis* and *Neisseria gonorrhoeae* from the same specimen. Because of its recent introduction into the market, experience with this assay is limited.

Other Tests

Chlamydia serology is of no value in the diagnosis of acute uncomplicated urogenital infections. High background prevalence and infrequent rises and falls in IgG and IgM make test results less meaningful. Serology is useful in the diagnosis of LGV and neonatal pneumonia.

Rapid clinic-based tests for chlamydia, e.g., *QuickVue*®, *Clearview*®, Biostar *OIA*®, Abbott *Testpack*®, are not recommended in clinical settings because their overall performance is inferior to currently available laboratory-based tests. In particular, they have a low sensitivity of approximately 50%.[25]

Treatment

The current CDC recommendations for the treatment of uncomplicated chlamydial infection include azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally 2 times a day for 7 days.[21] The results of clinical trials indicate that azithromycin and doxycycline are equally effective (95%) in eradicating infection.[29] These investigations were conducted primarily in populations in which adherence to a 7-day regimen was good.

Azithromycin has prolonged bioavailability, wide tissue distribution, high intracellular concentration, and high activity against chlamydia. However, it is more expensive than doxycycline. Azithromycin is now approved for use in persons less than 15 years of age. In populations with poor compliance with treatment or minimal follow-up, azithromycin may be more cost effective because it provides a single dose, directly observed therapy.[30]

Doxycycline has the advantage of low cost and a longer history of extensive use, but has the disadvantage of a longer course and resultant problems with adherence in certain populations.[31]

Alternative Regimens for Chlamydia

Alternative regimens include erythromycin base 500 mg orally 4 times a day for 7 days, erythromycin ethylsuccinate 800 mg orally 4 times a day for 7 days, ofloxacin 300 mg orally 2 times a day for 7 days, or levofloxacin 500 mg orally once a day for 7 days.[21] Erythromycin is less effective compared to azithromycin or doxycycline, and gastrointestinal side effects reduce compliance. A test of cure should be considered 3 weeks after completion of treatment with erythromycin.

Ofloxacin is similar in efficacy to doxycycline and azithromycin, but is more expensive. In cases where doxycycline and azithromycin are contraindicated, ofloxacin is a good alternative because of fewer gastrointestinal side effects. The efficacy of levofloxacin is based on its pharmacology and in vitro microbiological activity against *C. trachomatis*.

Antibiotic Resistance

Although rare cases have been reported, there has been no evidence of significant emergence of antibiotic resistance among *Chlamydia trachomatis* strains.

Presumptive Diagnosis and Treatment of Chlamydia

A presumptive diagnosis can be made and empiric treatment should be given at the time of the visit if patients present with syndromes consistent with chlamydial infection or are at high risk for chlamydial infection, such as reported sexual exposure to a case. The treatment will, in most of these cases, be instituted before test results

CDC Recommended Treatment for Uncomplicated Chlamydial Infections in Non-Pregnant Adolescents and Adults

Recommended Regimens:

Azithromycin	1 g orally single dose
or	
Doxycycline *	100 mg orally twice a day for 7 days

*Contraindicated in pregnant and nursing women and children under the age of 8.

CDC Alternative Recommended Treatment for Uncomplicated Chlamydial Infections in Non-Pregnant Adolescents and Adults

Alternate Regimens:

Erythromycin base	500 mg orally 4 times a day x 7 days
Erythromycin ethylsuccinate	800 mg orally 4 times a day x 7 days
Ofloxacin *	300 mg orally twice a day x 7 days
Levofloxacin *	500 mg orally once a day x 7 days

*Contraindicated in pregnant and nursing women.

are available. Criteria for presumptive treatment include: 1) a diagnosis consistent with urethritis or epididymitis in a male, 2) a diagnosis of mucopurulent cervicitis or PID in a female, 3) a sex partner with suspected or documented mucopurulent cervicitis, PID, urethritis, epididymitis, chlamydial or gonococcal infection, or 4) a sexual assault victim. In addition, patients with gonococcal infections should be concurrently treated for chlamydia. In cases that are diagnosed and treated presumptively, diagnostic testing is still important to document the infection, ensure adequate public health reporting and follow-up, reinforce partner notification, and enhance compliance with treatment, prevention interventions, and partner management.

TREATMENT KEY POINTS:

- Azithromycin and doxycycline are first-line treatments for chlamydial infection
- Azithromycin should be available for patients with potential poor adherence

Counseling, Testing, and Reporting

Counseling Messages

Patients diagnosed with chlamydial infection should be informed about the nature of the infection, modes of transmission, and the potential for long-term complications.

To minimize further transmission of infection and recurrent infection, patients treated for chlamydia should be instructed to abstain from sexual intercourse for 7 days after the single dose therapy, or until completion of the 7-day regimen and until 7 days after all of their sex partners have been treated.

A chlamydia diagnosis is an important opportunity to conduct risk reduction counseling. In a randomized controlled trial of STD/HIV counseling techniques, patients receiving brief risk counseling had 20% fewer STDs than patients receiving traditional didactic messages.[32]

Counseling should consist of reviewing the patient's protective behaviors, supporting patient-initiated behavior change, enhancing the patient's self perception of risk, identifying factors that affect risk behaviors, planning an acceptable and achievable risk reduction strategy, and providing referrals as indicated.

STD Testing

Patients who are found to be infected with chlamydia should be tested for gonorrhea and syphilis, and offered HIV testing.[21]

Chlamydia Reporting Requirements

Currently, every state has legislation requiring infectious disease reporting for sexually transmitted chlamydial infection. Patients who

are diagnosed and treated for chlamydia should be reported to the local health department where the patient resides.

KEY COUNSELING MESSAGES:

- Nature of chlamydial infection
- Medication use and possible side effects
- Abstinence for 7 days and until all partners have been treated
- Importance of partner treatment
- Risk reduction counseling
- Need for follow-up testing

Partner Management & Follow-Up Testing

The treatment of sex partners is essential to thwart acute infection and complications, interrupt further transmission, and reduce the risk of recurrent infection of the index patient. With every recurrent infection, the risk of serious complications increases significantly. Partners are often asymptomatic and therefore will not seek treatment without being notified.

All sexual contacts within the critical exposure period, typically within the past 60 days from the onset of symptoms or diagnostic test, need to be treated. If the patient reports no partners in the critical exposure period, the last sex partner should be treated. Partner referral may be conducted by patients or by providers or public health staff. Recent research has demonstrated that patient-delivered partner treatment may be an acceptable and effective strategy for reducing recurrent infection among some women.[33] Although this practice is currently allowed by California state law, practices and regulations in other states may vary.

Follow-up testing after treatment (test-of-cure) with doxycycline or azithromycin is not recommended unless symptoms persist or reinfection is suspected. However, a test-of-cure 3 weeks after completion of treatment should be considered if erythromycin is prescribed. Test-of-cure is recommended after treating pregnant women, regardless of the regimen used.

Several studies have demonstrated high rates of recurrent infection among young women within several months after treatment.[34-37] Up to 20% of treated patients will have a positive chlamydia test within 6 months after treatment. Although a few of these cases represent treatment failures, the vast majority are likely due to subsequent exposure to an infected partner. Thus, the CDC now recommends re-screening all women treated for chlamydia 3-4 months after the initial chlamydia episode.[21]

MANAGEMENT KEY POINTS:

- Counseling and partner management essential for reducing recurrent infection
- Test for concurrent STDs
- Re-screen female patients 3-4 months after treatment

Screening and Prevention

Prevention Strategies

Given the high prevalence of asymptomatic chlamydial infection and the high cost for treatment of the sequelae, prevention is imperative. Effective prevention requires a multi-pronged approach that includes counseling regarding abstinence and consistent and proper use of condoms, identification and treatment of asymptomatic infection among young sexually active women, treatment of male partners of infected women, and prompt recognition of clinical conditions such as cervicitis and urethritis.

Screening In Women

Screening programs are essential for reducing complications of chlamydia in individuals and reducing the reservoir of asymptomatic

SCREENING RECOMMENDATIONS

- Sexually active women 25 years of age and younger annually
- Sexually active women over 25 at high risk for chlamydial infection:
  - New or multiple sex partners and inconsistent or incorrect use of barrier contraceptives
  - History of recent STD, especially if in the past year
- Pregnant women, screen in the first trimester
- Any patient with diagnosed syphilis, gonorrhea or HIV infection

individuals who make up the majority of prevalent infections. Clinical settings that have routinely screened for chlamydia for several years have seen a decrease in chlamydia prevalence in their patient populations.[38-40] A randomized controlled trial of chlamydia screening and treatment in a health maintenance organization demonstrated a 56% reduction in the incidence of PID in the 12 months following this intervention.[41] Cost-effectiveness analyses have demonstrated that screening for chlamydia in populations with prevalence rates over 3-6% results in both cost savings and disease reduction.[42, 43]

The CDC and the U.S. Preventive Services Task Force recommend routine screening of all sexually active women 25 years of age and younger.[21, 44] Recently, the National Committee for Quality Assurance adopted chlamydia screening as a health care quality measure.[45] As a result, chlamydia screening of sexually active women patients ages 15-25 years will be included in the Health Plan Employer Data and Information Set (HEDIS), a set of performance measures used to assess the quality of care delivered by managed care organizations. HEDIS serves as a report card with which health insurance purchasers can evaluate the performance of competing managed care organizations.

For adolescent girls living in high prevalence areas, more frequent screening, such as every 6 months, may be appropriate.

Amplification tests provide the best sensitivity and specificity for purposes of screening asymptomatic populations, which equates to the best predictive values, particularly in low prevalence populations. Urine-based NAATs should be considered for screening females when a pelvic examination is not necessary. Other test technologies like EIA, DFA, and nucleic acid probes may offer acceptable predictive values in higher prevalence populations provided that appropriate quality assurance practices are followed.

Chlamydia screening of high risk populations in non-traditional settings appears to be a promising control strategy that expands access to underserved groups and avoids the expense of a clinic visit and examination by a health care professional.[46, 47]

Screening In Men

Chlamydia screening efforts in men have been limited by the discomfort of specimen collection

SCREENING KEY POINTS:

- Sexually active women age 25 and younger should be screened for chlamydia annually
- Screening programs prevent clinical complications, reduce prevalence in the community, and are cost effective
- NAATs are the best test for screening

for men (urethral swab) and the fact that cost effective strategies for male screening have not been developed. However, with the advent of non-invasive urine-based testing, screening men has become more feasible.[48] Given the route of transmission, screening and treatment of men infected with chlamydia would likely improve the health of the men screened, their partners, and their newborn infants; however, evidence-based guidelines are not yet available.

Chlamydia in Pregnancy

Approximately 3-10% of young pregnant women are infected with chlamydia. Although the vast majority of infections are asymptomatic, clinical presentations do not significantly differ in pregnancy.

Complications in Pregnancy

Up to one quarter of women with untreated chlamydial infection who undergo induced abortions develop endometritis and salpingitis. *C. trachomatis* may increase the risk of low birth weight, premature rupture of membranes, chorioamnionitis, and preterm delivery among infected mothers.[49-51] Post-partum chlamydial endometritis develops among 20-35% of infected pregnant women who deliver vaginally. Untreated chlamydial infections in pregnancy also may lead to transmission of infection to the neonate. Two-thirds of infants born to infected mothers develop conjunctivitis and/or pneumonia, as described earlier.

Treatment in Pregnancy

Recommended regimens for pregnant women include amoxicillin 500 mg orally 3 times daily for 7 days or erythromycin base 500 mg orally 4 times daily for 7 days.[21] Doxycycline and ofloxacin are contraindicated for pregnant women.

Although the safety and efficacy of azithromycin for pregnant and lactating women have not been definitively established, azithromycin 1 gm orally in a single dose is considered an acceptable treatment regimen in pregnant women. Additional alternatives include erythromycin base 250 mg orally 4 times daily for 14 days, erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days, or erythromycin ethylsuccinate 400 mg orally 4 times daily for 14 days. Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity.

CDC Recommended Treatment for Pregnant Women

Recommended Regimens:	
Erythromycin base	500 mg orally 4 times a day x 7 days
or	
Amoxicillin	500 mg orally 3 times a day x 7 days
Alternate Regimens:	
Erythromycin base	250 mg orally 4 times a day x 14 days
or	
Erythromycin ethylsuccinate	800 mg orally 4 times a day x 7 days
or	
Erythromycin ethylsuccinate	400 mg orally 4 times a day x 14 days
or	
Azithromycin	1 g orally single dose

Because of the lower efficacy of erythromycin and amoxicillin (80-85%), the lack of published efficacy data for azithromycin in pregnancy, and the importance of eliminating the infection, repeat testing of pregnant women is recommended 3 weeks after completing therapy. If using amplification tests, which detect nucleic acid, test-of-cure should be performed at least 3 weeks after completing therapy to avoid false positive results.

Screening in Pregnant Women

Prenatal screening for chlamydial infection is recommended to prevent pregnancy and neonatal complications due to chlamydial infection. First trimester screening is recommended for all pregnant women.[21] In addition, pregnant women age 25 or younger or with high risk sexual behaviors (e.g. new or multiple sexual partners) should also be screened during the third trimester to insure adequate treatment and reduce the risk of reinfection before delivery.[21, 44, 52]

Chlamydia in Children and Neonates

Most vaginal and rectal infections in boys and girls are asymptomatic. Although chlamydial infection in children may be an indication of sexual abuse, vaginal and rectal infection as a result of perinatal transmission has been documented. Perinatal colonization can persist for as long as 3 years.

The evaluation for sexual abuse should be performed in consultation with an expert. Many of the diagnostic tests discussed above have not been validated for testing in children. Culture is considered the gold standard and is recommended for medicolegal purposes because of its near perfect specificity. Expert opinion suggests that nucleic acid amplification tests may be an alternative only if cultures are unavailable and confirmatory testing is performed.

Treatment in Children

Treatment regimens vary by age and weight of the child.[21] For children less than 45 kg, erythromycin base or erythromycin ethylsuccinate (EES) is recommended. For children at least 45 kg in weight and less than 8 years old, azithromycin 1 gram orally in a single dose is appropriate. Children at least 8 years old should be given azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice daily for 7 days.

CDC Recommended Treatment for Children

Children < 45 kg

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

Children ≥ 45 kg and < 8 Years of Age

Azithromycin 1 g orally single dose

Children ≥ 8 Years of Age

Azithromycin 1 g orally single dose

or

Doxycycline 100 mg orally twice a day x 7 days

* Erythromycin base or erythromycin ethylsuccinate.

Treatment in Neonates

Neonates with chlamydia conjunctivitis or pneumonia should be treated with erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into 4 equal doses for a total of 10-14 days.[21] Oral medication is necessary for conjunctivitis; topical antibiotic therapy is inadequate. Efficacy of treatment for conjunctivitis and pneumonia is only 80%, and follow-up is necessary to assess resolution. A second course of therapy may be required.

An association between oral erythromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants less than 6 weeks of age who were treated with the drug. Infants treated with erythromycin should be followed for signs and symptoms of IHPS. Data on use of other macrolides (azithromycin or clarithromycin) for the treatment of neonatal chlamydia infection are limited.

CDC Recommended Treatment for Neonatal Infections

Erythromycin*	**50 mg/kg/day orally divided into 4 doses for 10-14 day**

* Erythromycin base or erythromycin ethylsuccinate.

Chlamydia & HIV

Symptomatic genital chlamydial infection has been shown to increase the amount of HIV in genital secretions, which may increase the likelihood of HIV transmission. Genital chlamydial infection also increases the susceptibility to HIV infection by increasing the number of target inflammatory cells in the genital area.[53] It is not clear whether asymptomatic infection increases transmissibility of or susceptibility to HIV infection.

Patient education about symptoms of infection and early empiric treatment of symptomatic individuals may be important to reduce HIV transmission. Because chlamydial infection is generally asymptomatic, the CDC recommends annual chlamydia screening of all HIV-infected individuals, with more frequent screening indicated in some situations.[54]

Clinical manifestations of chlamydial infections among HIV-infected patients do not differ from those among non-HIV-infected patients. Further, treatment of chlamydial infection in HIV-infected individuals is the same as for non-HIV-infected persons and includes the standard CDC-recommended therapies.

Conclusions

Sexually transmitted *Chlamydia trachomatis* is the most common reportable communicable disease in the United States. Although it can produce a variety of clinical syndromes, the majority of infection is asymptomatic and goes undetected. Up to 40% of women with untreated cervical chlamydial infection will develop PID, the leading cause of preventable infertility among women. Early identification through routine screening and appropriate treatment can significantly reduce the short- and long-term complications in women and neonates.

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