

# Chlamydia

## Learning Objectives

Upon completion of this module the learner will be able to:

1. Describe the epidemiology of chlamydia.
2. Identify the clinical manifestations of chlamydia-related syndromes in adults and infants.
3. State the advantages and disadvantages of laboratory methods available to diagnose chlamydial infections.
4. Perform appropriate screening and sample collection strategies.
5. List the current recommended treatments for chlamydia and related syndromes.
6. Summarize the clinical and community-based strategies for chlamydia prevention to include counseling messages and partner management.

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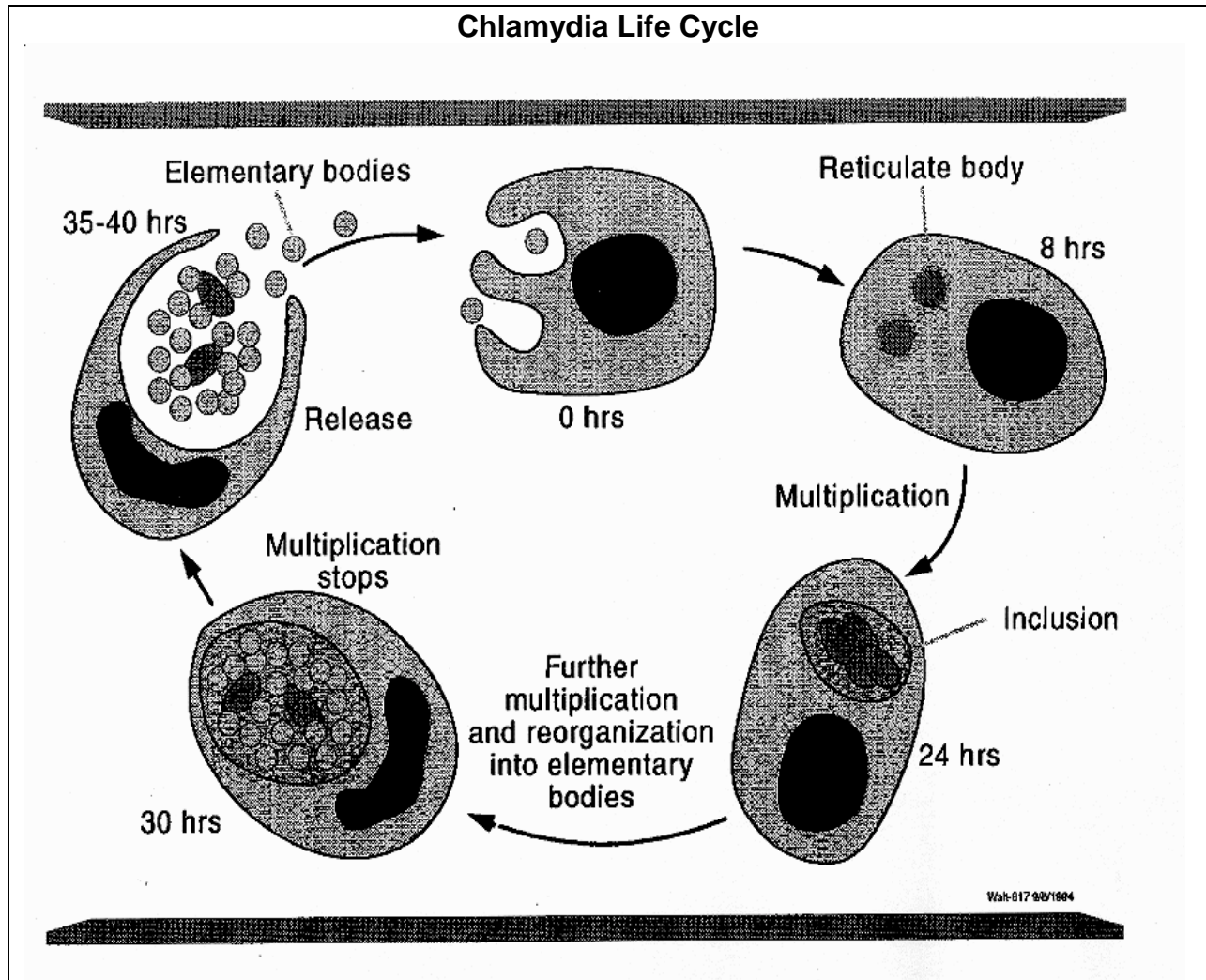
# **CHLAMYDIA TRACHOMATIS GENITOURINARY TRACT INFECTIONS**

## **I. Epidemiology**

- A. Incidence: approximately 3-4 million estimated cases in USA per annum.
- B. Prevalence in selected populations:
  - 1. STD clinics: 7-25%.
  - 2. Family planning: 3 -15%.
  - 3. Prenatal clinics: 5 -10% sometimes 15%.
  - 4. Managed care or private practice: 3 - 5%.
  - 5. Youth detention facilities: 10 -20%
  - 6. School-based clinics: 5 – 15%
  - 7. Homeless youths: 10 –15%
  - 8. Decreasing prevalence in selected areas with control programs that include clinic-based screening.
- C. Risk factors: adolescence, new or multiple sexual partners, cervical ectopy (often related to OC use/adolescence), lack of barrier contraceptive.
- D. Transmission:
  - 1. Exact rates unknown. Up to 68% from men to women.
  - 2. High prevalence of coinfection in partners (>50%).
  - 3. Significant asymptomatic reservoir exists in the population.
  - 4. Re-infection is common.

## **II. Pathogenesis**

- A. Microbiology:
  - 1. Obligate intracellular bacterium, has DNA and RNA, bacterial ribosomes, Gram-negative-like cell wall, susceptible to antibiotics.
  - 2. Life cycle: unique, requires 36-48 hours.
  - 3. Generally causes superficial mucosal infection of columnar epithelial cells, often chronic (months to years). LGV strains can also infect stratified squamous epithelium.
  - 4. Chlamydia life cycle: see figure.



**B. Taxonomy:**

1. Genus:

- a) *C. trachomatis*.
- b) *C. psittaci*.
- c) *C. pneumoniae*.

2. Serovars:

- a) A, B, Ba, C (trachoma).
- b) D-K (genitourinary and ocular infections).
- c) L<sub>1</sub>-L<sub>3</sub> (Lymphogranuloma venereum).

3. Biovars: lymphogranuloma venereum (LGV) associated vs. non-LGV associated.

### III. Clinical Manifestations

**Summary of Clinical Syndromes Caused by *C. trachomatis***  
**Local Infection                      Complication                      Sequelae**

	Local Infection	Complication	Sequelae
Men	Conjunctivitis	Reiter's syndrome	
	Urethritis	Epididymitis	
	Proctitis		
Women	Conjunctivitis	Endometritis	Infertility
	Urethritis	Salpingitis	Ectopic pregnancy
	Cervicitis	Perihepatitis	Chronic pelvic pain
	Proctitis	Reiter's syndrome	
Infants	Conjunctivitis		
	Pneumonia	Chronic lung disease ?	
	Pharyngitis, Rhinitis		

#### A. Genital infection in men:

##### 1. Urethritis.

- a) Majority (>50%) asymptomatic.
- b) Incubation period unknown (probably 5-10 days in symptomatic infection).
- c) Symptoms/signs: discharge, dysuria, urethral discharge on exam.

## 2. Complications

### a) Epididymitis:

- 1) Infrequent but most common local complication in males.
- 2) Up to 70% of sexually transmitted cases due to CT, others to GC; some cases have both pathogens; it is important to distinguish sexually transmitted cases in heterosexuals (CT/GC) and men who have sex with men (*E. coli*, GC) from non-sexually transmitted epididymitis (*E. coli*, pseudomonas), which is more common in older men.
- 3) Bacterial etiology varies by sexual behavior and age.
- 4) Symptoms/signs: fever, epididymal/testicular pain, evidence of NGU, epididymal tenderness/mass on exam.

### b) Reiter's syndrome:

- 1) Immune response following infection with CT resulting in an inflammatory process.
- 2) Characteristic syndrome of conjunctivitis, urethritis, oligoarthritis and skin lesions (keratoderma blenorrhagica and circinate balanitis) occurring 3 to 6 weeks after genital chlamydial infection.
- 3) Chlamydial antigens and DNA present within joints.
- 4) Affects predominantly males, especially HLA-B27+.
- 5) Use of long-term antibiotic treatment under study. Does not respond to short courses of antibiotics as this is a complex disease process resulting from CT infection.

## 3. Possible sequelae:

- a) Role for chlamydial infection in male sterility is unproven.
- b) Risk of prostatitis is unknown.

## B. Genital infections in women:

### 1. Cervical Infection:

- a) Frequency of infection at cervical site 75-80%.
- b) 70% to 80% of cervical infections are without associated symptoms or signs.
- c) When present, symptoms are non-specific.
- d) About 30% have specific signs of mucopurulent cervicitis including mucopurulent endo-cervical discharge, edematous cervical ectopy with spontaneous or easily induced endo-cervical bleeding.

### 2. Urethral Infection:

- a) Frequency of infection at urethral site is 50%, based on screening studies in STD clinics.
- b) Usually asymptomatic.
- c) May cause the "dysuria-pyuria" syndrome mimicking acute cystitis, symptoms include dysuria and frequency, often in young women with recent new sexual partner.

3. Complications:
  - a) Pelvic inflammatory disease (PID):
    - 1) Classically, CT-associated PID is clinically milder than GC-associated PID.
    - 2) Substantial proportion of CT-associated PID is clinically silent.
    - 3) Symptoms/signs: lower abdominal pain, cervical motion tenderness and adnexal tenderness on pelvic exam.
  - b) Perihepatitis:
    - 1) Inflammation of the liver capsule.
    - 2) Initially attributed to gonococcal infection but now more often (up to 70%) associated with chlamydial disease.
    - 3) Characterized by right upper quadrant pain, nausea, vomiting, fever, evidence of PID on exam.

C. Syndromes seen in men or women:

1. Conjunctivitis:
  - a) Can occur as a result of autoinoculation from infected genitalia in adults, and by passage through an infected birth canal for neonates.
  - b) Signs/symptoms: conjunctiva in adults often has a follicular appearance and the secretions are not purulent; can cause purulent conjunctivitis in the neonate 5 to 14 days after delivery.
2. Rectal infection:
  - a) Due to non-LGV serovars.
  - b) Signs/symptoms: rectal pain, discharge, abnormal anoscopy (mucopurulent discharge, pain, spontaneous or induced bleeding).
  - c) Infection seen in persons practicing receptive anal sex.
  - d) Colonization due to cervical infection in women is 25-30%, but generally doesn't lead to symptomatic disease.
3. Proctocolitis:
  - a) Due to LGV serovars (L1, L2, L3).
  - b) Signs/symptoms: severe rectal pain, discharge, hematochezia, markedly abnormal anoscopy with lesions extending into colon, fever, lymphadenopathy.
  - c) If untreated, may lead to bowel obstruction
4. Inguinal adenopathy:
  - a) Due to LGV serovars (L1,L2, L3).
  - b) Sign/symptoms: often the presenting symptom is multiple, enlarged, matted, tender inguinal lymph nodes which may be suppurative and are usually bilateral; rarely presents as a genital ulcer; lesions characterized as superficial, painless, usually singular, variable base without induration.

#### D. Chlamydial infections in infants and children:

1. Perinatal: most common clinical manifestations:
  - a) Inclusion conjunctivitis:
    - 1) Occurrence: 5-14 days after delivery.
    - 2) Signs and symptoms range from mild with scant mucoid discharge to severe with copious purulent discharge, chemosis, and pseudomembrane formation, erythema, friability, edema.
  - b) Pneumonia:
    - 1) Occurrence: 4-12 weeks after delivery.
    - 2) Signs and symptoms: cough and congestion, afebrile, tachypnea, auscultation of rales.
2. Infections in pre-adolescent males and females:
  - a) Most vaginal and rectal infections in boys and girls are asymptomatic.
  - b) Vertical transmission: it is important to remember that vaginal and/or rectal infection as a result of perinatal transmission has been documented. Colonization can persist for as long as 2 to 3 years and may not indicate sexual abuse or assault.
  - c) Sexual abuse: the evaluation should be performed by, or in consultation with, an expert in the assessment of child sexual abuse. If STD testing is indicated, because of the legal and psychosocial consequences of a false-positive diagnosis, only tests with high specificities should be used. The CDC recommends performing cultures for Ct from specimens collected from the anus in both boys and girls and from the vagina in girls. Expert opinion suggests that nucleic acid amplification tests (NAATs) may be an alternative ONLY if cultures are unavailable and if confirmation by a second FDA approved NAAT that targets a different molecule from the initial test is available.

#### IV. Diagnostic Testing

##### A. Gram-stained smear:

1. Chlamydial elementary bodies are Gram-negative and do not take the counterstain, therefore are not visible with this technique.
2. From male urethral exudate  $\geq 5$  PMNs/oif in the absence of Gram-negative intracellular diplococci (GNID) is diagnostic for NGU and may be predictive for CT, depending on disease prevalence (see urethritis module).

3. There are no standardized criteria for the Gram stain (in terms of number of leukocytes) to identify mucopurulent cervicitis (MPC), which may be predictive of CT, also depending on disease prevalence (see MPC module).

B. Culture:

1. Expensive and technically difficult.
2. Rigorous transport requirements: requires refrigeration and rapid transport to lab within 48 hours.
3. Involves the use of live cells and monoclonal antibody staining.
4. Performance varies widely among labs; for general performance characteristics, see Chlamydia Test Performance Characteristics Table.
5. Approved for use in all anatomical sites.
6. Adequate numbers of columnar epithelial cells must be obtained.

C. Non-culture tests:

1. Rely on detection of bacterial products (proteins, nucleic acid) in patient samples:
  - a) Non-amplified tests:
    - 1) Antigen detection methods (Enzyme Immuno Assay – EIA, e.g., *Chlamydiazyme*®; Direct Fluorescent Antibody test – DFA, e.g., *Microtrack*®).
      - (a) Do not require live organisms; therefore, less expensive, less technically demanding.
      - (b) Detect elementary body components through immunologic means.
      - (c) For comparative performance, see Chlamydia Test Performance Characteristics Table.
      - (d) DFA is the only test that can provide simultaneous measure of the adequacy of the specimen through detection of columnar cells.
    - 2) Nucleic acid hybridization (DNA Probe, e.g., GenProbe *Pace 2* ®):
      - (a) Detects chlamydia-specific nucleic acids.
      - (b) In general, performance characteristics similar to EIA (see Chlamydia Test Performance Characteristics Table).
    - 3) General considerations:
      - (a) Non-amplified tests require adequate numbers of protein or DNA to detect presence of CT.
      - (b) EIA is approved for urethral, cervical, and conjunctival sites.
      - (c) DFA is approved for urethral, cervical, rectal, and conjunctival sites.

b) Amplified tests:

- 1) Nucleic acid amplification tests – NAAT (Polymerase Chain Reaction-PCR, e.g., Roche Amplicor®; Transcription Mediated Amplification-TMA, e.g., GenProbe *AmpCT*, *APTIMA*®; Ligase Chain Reaction-LCR, e.g., Abbott LCX®; Strand Displacement Amplification – SDA, e.g., BD *ProbeTec*®).
- 2) Markedly amplifies target nucleic acids (DNA, RNA) and increases the sensitivity to >90% for cervical and urethral swabs.
- 3) Specificity >99%.
- 4) All can be used on first 10-15 cc of urine specimens from men and women. (Must be > 2 hours after last void).
- 5) Self-collected vaginal swabs may offer another sensitive specimen for NAAT testing (although not currently FDA approved).
- 6) For general performance characteristics, see Chlamydia Test Performance Characteristics Table.

### Chlamydia Test Performance Characteristics

Test	Sensitivity* *	Specificity	Detectability Level (Elementary Bodies)
Enzyme Immunoassay	40% - 60%	99.5%*	1,000 - 10,000
Non-Amplified Genetic Probe	40% - 65%	99.0%	1,000 - 10,000
Direct Fluorescent Antibody	50% - 70%	99.8%	1,000 to 10,000
Cell Culture	50% - 90%	99.9%	10 - 100
Nucleic Acid Amplification Tests (NAATs) Ligase Chain Reaction (LCR); Polymerase Chain Reaction (PCR); Transcriptase Mediated Amplification (TMA); Strand Displacement Amplification (SDA)	Over 90% for cervical, urethral and urine testing	99.7%	1 - 10

\*Specificity using confirmatory assays.

\*\*Defined using a combination of different test methodologies, including culture, DFA, and PCR or LCR directed against a target sequence distinct from that used in the routine PCR or LCR assays.

D. Serology:

For uncomplicated genital infections caused by CT, it is rarely of value.

For the diagnosis of LGV, complement-fixation test titers of 1:64 or greater (titers of >256 strongly support a diagnosis and titers of  $\leq 32$  rule it out).

E. Rapid tests (e.g., *Clearvue*®): none have adequate sensitivity as yet; currently not recommended.

## V. Treatment

A. Treatment of uncomplicated genital chlamydial infections, 2001:

1. CDC-recommended regimens:

Azithromycin, 1.0 gram orally in a single dose, **or**  
Doxycycline 100 mg orally twice daily for 7 days.

2. Alternative regimens:

Erythromycin base 500 mg orally four times a days for 7 days, **or**  
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days, **or**  
Ofloxacin 400 mg orally twice a day for 7 days, **or**  
Levofloxacin 500 mg orally once a day for 7 days.

B. Treatment of chlamydial infection in pregnant women:

1. CDC-recommended regimens:

Erythromycin base 500 mg orally four times a day for 7 days, **or**  
Amoxicillin 500 mg orally three times a day for 7 days.

2. Alternative regimens:

Erythromycin base 250 mg orally four times a day for 14 days, **or**  
Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days, **or**  
Erythromycin ethylsuccinate 400 mg orally four times a days for 14 days, **or**  
Azithromycin 1.0 gram orally in a single dose\*

\*Data are insufficient to recommend the routine use in pregnant women. However, clinical experience of some experts and preliminary data suggest that azithromycin is safe and effective.

3. Erythromycin estolate is contraindicated during pregnancy because of drug-related hepatotoxicity.

C. Treatment of neonatal conjunctivitis and/or pneumonia:

1. CDC-recommended regimen:

\*Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days.\*\*

\* 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 and clarithromycin) for the treatment of neonatal chlamydia 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.

\*\*The effectiveness of erythromycin is approximately 80%; a second course of therapy may be required.

2. Prophylactic antibiotic treatment for infants born to mothers who have an untreated chlamydial infection is not indicated. Infants should be monitored to ensure appropriate treatment if infection develops.

D. Treatment of chlamydial infection in children:

CDC-recommended regimens:

1. Children who weigh <45 kg:

Erythromycin base or ethylsuccinate 50 mg/day orally divided into four doses daily for 14 days.

2. Children who weigh  $\geq$  45 kg, but are < 8 years of age:

Azithromycin 1.0 gram orally in a single dose.

3. Children  $\geq$  8 years of age:

Azithromycin 1.0 gram orally in a single dose, **or**  
Doxycycline 100 mg orally twice a day for 7 days.

E. Treatment of lymphogranuloma venereum:

1. CDC-recommended regimen:

Doxycycline 100 mg orally twice a day for 21 days.

2. Alternative regimen:

Erythromycin base 500 mg orally 4 times a day for 21 days.

3. Some experts believe azithromycin 1.0 gram orally once weekly for three weeks is likely to be effective, although clinical data are lacking.

F. No clinically significant emergence of drug resistance among CT strains.

G. Patients should be instructed to abstain from sexual intercourse until partners are

cured and for seven days after a single dose of azithromycin or until completion of a seven-day regimen.

H. Repeat testing after treatment for a chlamydial infection.

1. Pregnant women: repeat testing, preferably by culture, 3 weeks after completion of therapy.
2. Consider test of cure 3 weeks after completion of therapy any time erythromycin is used.
3. All adolescents, and women older than age 20 at increased risk for infection, should be encouraged to return for repeat screening 3-4 months after a chlamydial infection.

## VI. Prevention and Counseling

A. Screening (testing of asymptomatic individuals): screening for chlamydia has been found to reduce the incidence of pelvic inflammatory disease in women, complications in the individual, and the burden of disease in the community.

1. For women:

Universal screening of sexually active individuals age 25 and under should be done annually. Supported by the CDC and the US Preventive Services Task Force (USPSTF). A Health Employer Data and Information Set (HEDIS) quality measure for managed care plans for chlamydia screening has been developed by NCQA. This HEDIS indicator measures the proportion of sexually active females between the ages of 15 and 25 who were screened for chlamydia.

2. For men:

The role of routine chlamydia screening in sexually active men is currently under investigation.

B. Partner management:

Patients should be instructed to refer their sex partners for evaluation, testing and treatment. Because exposure intervals have received limited evaluation, the following recommendations are somewhat arbitrary:

1. Sex partners should be evaluated, tested and treated if they had sexual contact with the patient during the 60 days preceding onset of symptoms in the patient or diagnosis of chlamydia.
2. The most recent sex partner should be evaluated and treated even if the time of the last sexual contact was >60 days before symptoms appeared.

C. Reporting:

Laws and regulations in all states require that persons diagnosed with chlamydia are reported to public health authorities by clinicians, labs, or both.

D. Patient counseling and education:

1. Nature of the infection:

- a) Asymptomatic infection is common among both men and women.
- b) There is an increased risk of upper tract damage with re-infection.

2. Transmission issues:

- a) Effective treatment of chlamydia may reduce HIV transmission.
- b) Patients should be instructed to 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 index patient.

3. Risk reduction:

- a) Assess client's behavior-change potential.
- b) Discuss prevention strategies (abstinence, monogamy, condoms, limit number of sex partners, etc.). Latex condoms, when used consistently and correctly, can reduce the risk of transmission of chlamydia.
- c) Develop individualized risk-reduction plans.

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