

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, barrier contraception, and partner management

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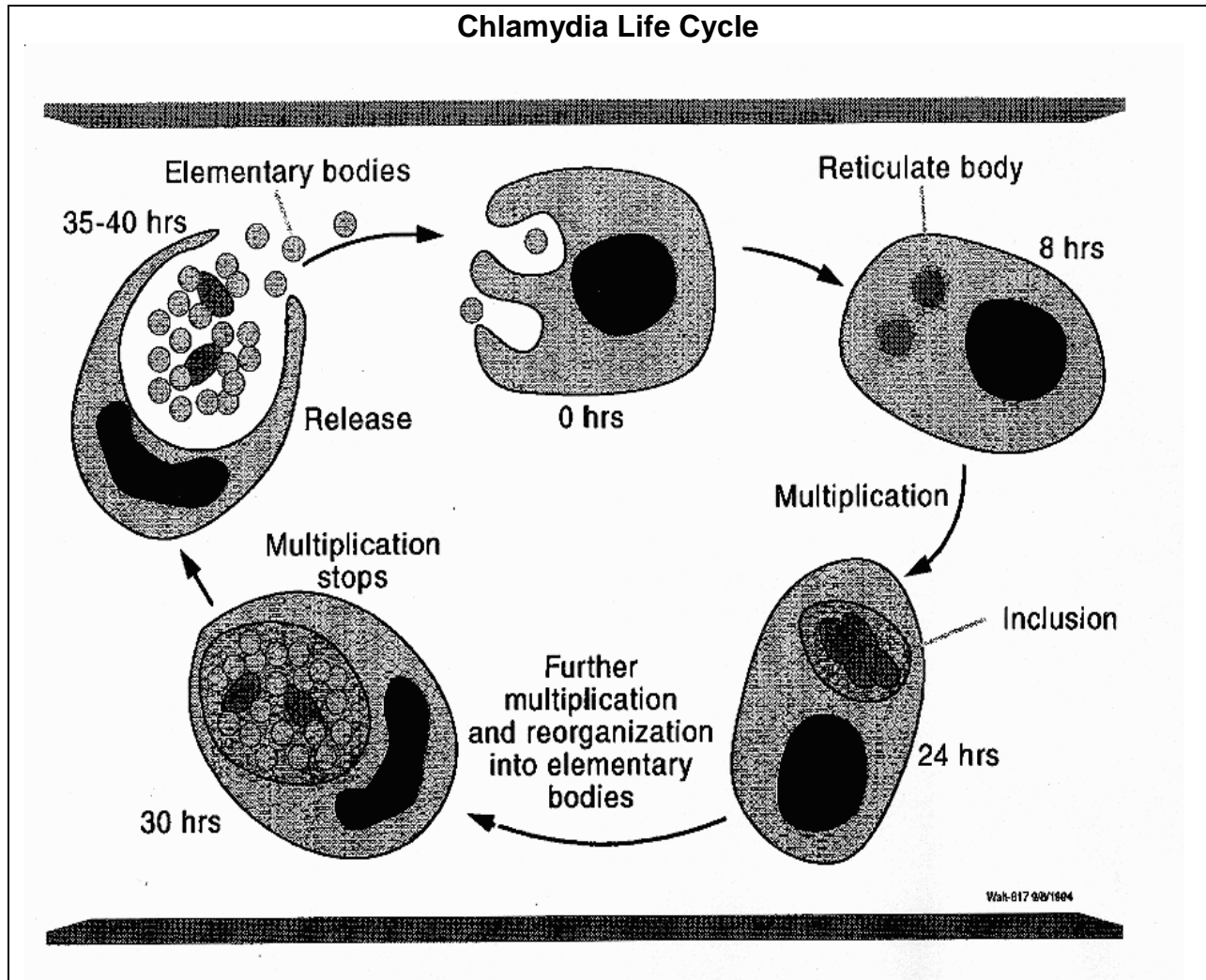
CHLAMYDIA TRACHOMATIS GENITOURINARY TRACT INFECTIONS

I. Epidemiology

- A. Incidence: approximately 3-4 million estimated cases in USA per year.
- 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 (young women): 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, prior chlamydial infection, new or multiple sexual partners, cervical ectopy (often related to OC use/adolescence), lack of barrier contraceptive
- D. Transmission:
 - 1. Exact rates unknown, but high prevalence of coinfection in partners (50-75%)
 - 2. Significant asymptomatic reservoir exists
 - 3. Re-infection is common in women and men

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 for completion
 - 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. Species :

- a) *Chlamydia trachomatis*
- b) *Chlamydophila psittaci*
- c) *Chlamydophila pneumoniae*

Current taxonomy of the non-trachomatis species remains an area of active discussion

2. Serovars of *C. trachomatis* (based on major outer membrane protein composition):

- a) A, B, Ba, C (trachoma)
- b) D, Da, E, F, G, H, I, Ia, J, Ja, K (genitourinary and ocular infections)
- c) L1, L2, L2a, L2b, L3 (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			
	Urethritis		Epididymitis Reactive arthritis	Infertility
	Proctitis			
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Women	Conjunctivitis			
	Urethritis			
	Cervicitis		Pelvic Inflammatory Disease Reactive arthritis	Infertility Ectopic pregnancy Chronic pelvic pain
	Proctitis			
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Infants	Conjunctivitis			
	Pneumonia		Chronic lung disease ?	
	Pharyngitis Rhinitis			

A. Genital infection in men:

1. Urethritis.

- a) Majority (>50%) asymptomatic
- b) Incubation period unknown (probably 7-14 days in symptomatic infection)
- c) Symptoms: urethral discharge, dysuria

d) Signs: urethral discharge

DRAFT

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*, CT, GC) from non-sexually transmitted epididymitis, the latter which is more common in older men with urinary tract abnormalities and the pathogens are typically coliform bacteria (e.g., *E. coli*) or *Pseudomonas* spp.
- 3) Bacterial etiology varies by sexual behavior and age.
- 4) Symptoms: epididymal/testicular/scrotal pain, fever (occasionally).
- 5) Signs: scrotal erythema/swelling/tenderness, epididymal tenderness/mass, Gram stain evidence of NGU, hydrocele (occasionally).

3. Possible sequelae:

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

B. Genital infections in women:

1. Cervical Infection:

- a) 70% to 80% of cervical infections are without associated symptoms or signs.
- b) When present, symptoms are non-specific.
- c) About 5-10% of asymptomatic chlamydia-infected women (undergoing screening with a nucleic acid amplification test) have specific signs of mucopurulent cervicitis including mucopurulent endocervical discharge and/or easily induced endocervical bleeding

2. Urethral Infection:

- a) Frequency of co-infection at urethral site is about 65%, based on screening studies (primarily utilizing chlamydia culture) in STD clinics.
- b) Usually asymptomatic
- c) May cause the “dysuria-pyuria” syndrome (aka, “acute urethral 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: lower abdominal or pelvic pain, nausea, vomiting (occasionally), fever (occasionally).
 - 4) Signs: cervical motion tenderness, fundal tenderness, adnexal tenderness on pelvic exam
 - b) Perihepatitis (i.e., Fitz-Hugh-Curtis Syndrome):
 - 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. Non-LGV Serovar Rectal infection:
 - a) Frequently asymptomatic
 - b) Symptoms: rectal pain, discharge, tenesmus
 - c) Signs: abnormal anoscopy (mucopurulent discharge, pain, spontaneous or induced bleeding)
 - d) Infection seen in persons practicing receptive anal sex
 - e) Concomitant infection of the rectum occurs in about 25-30% of women with cervical chlamydial infection, and generally is asymptomatic.
3. LGV Proctocolitis:
 - a) Due to LGV serovars
 - b) Symptoms: severe rectal pain, discharge, hematochezia, tenesmus, fever
 - c) Signs: markedly abnormal anoscopy with lesions extending into colon, fever, lymphadenopathy
 - d) If untreated, may lead to complications, including bowel obstruction, fissures, and fistulas

4. Inguinal adenopathy:
 - a) Due to LGV serovars
 - 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.
5. Reactive arthritis:
 - a) Immune response following a trigger infection (chlamydia or dysentery) resulting in an inflammatory process
 - b) Characteristic syndrome of conjunctivitis, urethritis or cervicitis, oligoarthritis (asymmetric) and skin lesions (keratoderma blenorrhagica and circinate balanitis [in men]) occurring 3 to 6 weeks after trigger infection
 - c) Chlamydial antigens and DNA have been demonstrated within joints
 - d) Affects predominantly males and associated with HLA-B27
 - e) HLA-B27+ subjects have more severe disease course
 - f) Use of long-term antibiotic treatment under study. Does not always respond to short courses of antibiotics as this is a complex disease process resulting from CT infection.

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 (Afebrile Pneumonia Syndrome [APS]):
 - 1) Occurrence: 4-12 weeks after delivery
 - 2) Signs and symptoms: cough and congestion, afebrile, tachypnea, auscultation of rales
 - 3) May predispose to chronic or recurrent obstructive airway disease
2. Infections in pre-adolescent males and females:
 - a) Most genital and rectal infections in boys and girls are asymptomatic.

- b) Vertical transmission: it is important to remember that genital 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 ≥ 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. Used on genital or rectal specimens
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., Gen-Probe *APTIMA*® CT and *APTIMA*® Combo 2; Strand Displacement Amplification – SDA, e.g., Becton Dickinson *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 10-15 cc of first-void urine specimens from men and women (must be >1 hour after last void)
 - 5) Self-collected vaginal swabs offer another sensitive specimen for NAAT testing and using them is highly acceptable to most women. The Gen-Probe *APTIMA*® is the only FDA approved test for use on vaginal swab specimens.

- 6) NAATs have higher sensitivity than culture for CT detection in anorectal and oropharyngeal swab specimens, but are not FDA-cleared for use with these specimens. Some laboratories have met CLIA requirements and have validated NAAT testing on anorectal swab specimens.
- 7) Liquid-based cytology specimens collected for Pap smears might be acceptable specimens for NAAT testing, although test sensitivity using these specimens might be lower than for cervical swab specimens. CT testing from the ThinPrep® Pap Test collection vial is FDA approved with the Amplicor® and APTIMA® Combo 2 assays.
- 8) For general performance characteristics, see Chlamydia Test Performance Characteristics Table below.

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) Polymerase Chain Reaction (PCR); Transcriptase Mediated Amplification (TMA); Strand Displacement Amplification (SDA)	Over 90% for cervical, vaginal, 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 ≤32 rule it out). See module on GUD for more information on the laboratory diagnosis of LGV.

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

V. Treatment (2010 CDC STD Treatment Guidelines)

A. Treatment of uncomplicated genital chlamydial infections:

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. Recommended regimens:

Azithromycin 1.0 gram orally in a single dose, **or**
Amoxicillin 500 mg orally three times a day for 7 days

2. Alternative regimens:

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

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

C. Treatment of neonatal conjunctivitis and/or pneumonia:

1. 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:

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. 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 they and their partners have completed a CDC-recommended CT treatment regimen; this may be either 7 days after a single dose of azithromycin or until completion of a CDC-recommended 7-day CT treatment regimen.

H. Repeat testing after treatment for a chlamydial infection.

1. Pregnant women: repeat testing by NAAT at least 3 weeks after completion of therapy
2. Consider test of cure 3 weeks after completion of therapy any time erythromycin is used
3. All women and men with chlamydial infection should be encouraged to return for repeat testing at approximately 3 months after treatment

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 and the prevalence of chlamydia in the community.

1. For women:

Universal screening of sexually active individuals age 25 and under should be done annually and is supported by the CDC, the US Preventive Services Task Force (USPSTF; age 24 and under in the USPSTF guidelines), the American Medical Association, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the American Academy of Family Physicians. 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. NAAT is the recommended screening test, and a vaginal swab (provider- or patient-collected) is the recommended specimen for screening with NAAT. Endocervical swab and first-void urine specimens are also acceptable for screening with NAAT.

2. For men:

The role of routine chlamydia screening in sexually active men remains under investigation. In a Male Chlamydia Screening Meeting Report released by the CDC in 2007 (<http://www.cdc.gov/std/chlamydia/ChlamydiaScreening-males.pdf>), there are recommendations for targeted chlamydial screening of males using NAAT on first-void urine specimens for programs that have already undertaken or are considering such an effort. The focus of screening should be on venues with high chlamydial prevalence, such as STD clinics and correctional facilities.

B. Partner management:

1. Partner Referral:

This method of partner management remains the standard of care. Patients should be instructed to refer their sex partners for evaluation, testing and treatment. Although exposure intervals have received little formal evaluation, the CDC recommends the following:

- a. 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.
- b. 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.

2. Expedited Partner Therapy (EPT):

This approach encompasses the provision of medication or a prescription to a partner by the patient or provider. There are potential advantages (e.g., more partners receiving treatment, etc.) and disadvantages (e.g., legal constraints, etc.) to this approach that are under investigation. In instances where standard partner referral may not be feasible, EPT may be considered an option for partner management of heterosexual male or female patients with chlamydia, especially in states where EPT is permissible or potentially allowable (<http://www.cdc.gov/std/ept/legal/default.htm>).

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 or acquisition
- 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 reducing the risk of re-infecting the index patient.

3. Risk reduction:

- a) Assess client's behavior-change potential
- b) Discuss prevention strategies (abstinence, monogamy, condoms, limiting the 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

VII. References:

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