# Review on Genital Chlamydia Trachomatis Infection

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## ABSTRACT

*Chlamydia trachomatis infection is a common sexually transmitted disease worldwide. The genital infection can result in serious complications and sequelae such as infertility and ectopic pregnancy. However, early identification of infected women is difficult because symptoms of the infection are usually nonspecific and up to 70% infections in women are asymptomatic and persistent for months to years. Apart from cervicitis and urethritis, it may also cause pelvic inflammatory disease, Bartholin's gland abscess, epididymitis, and various complications of pregnancy. Fortunately, chlamydial infection is an easily treatable disease. Therefore, effort should be paid on appropriate prescreening of patients at risk and and risk reduction interventions.*

**Keywords:** Chlamydia trachomatis, urethritis, cervicitis, pelvic inflammatory disease

## INTRODUCTION

*Chlamydial trachomatis* is a unique bacterium in that it is a true parasite with an extracellular and intracellular phase of its life cycle. It has a specific requirement for adenosine triphosphate, which it must obtain from the host. Its ability to colonize a host and inflict significant tissue damage is thought to be responsible for a large number of cases of infertility and ectopic pregnancies.

Chlamydial infection has been linked to urethritis, proctitis, epididymitis, Bartholin's gland abscess, cervicitis, endometritis, salpingitis, perihepatitis, choriaoamnionitis, premature rupture of membranes, and premature delivery. This organism has also been linked, primarily through serologic association, to infertility and ectopic pregnancy.

## EPIDEMIOLOGY

*Chlamydia trachomatis* is the commonest sexually transmitted bacterial pathogen worldwide. Approximately 4 million new cases occur each year in the United States at an estimated total cost of $2.4 million.[1] In reference to various prevalence studies carried out in selected populations in the developed countries, the higher prevalence of genital chlamydial infection were found in the sexually active females (>10%) and patients attending sexually transmitted disease clinics (5-15%).[1,2] The rate is usually found to be <5% in adult women during routine check-up.[3,4] Although fewer studies have been reported for men, prevalence range from 15-20% among men seen in sexually transmitted disease clinics and from 3-5% among young asymptomatic men seen in general medical settings.[5-7]

Genital chlamydial infection is also the commonest cause of pelvic inflammatory disease (PID) in developed countries. Cervicitis caused by the organism is complicated by PID in 8-10% of teenage girls, then the risk decreases with increasing age.[8] An estimated 15-40% of women with cervical chlamydial infections develop pelvic inflammatory disease (PID) that leads to serious sequelae.[9,10] Approximately 20% of women with laparoscopically confirmed PID will have infertility, 18% will have chronic pelvic pain and 10% will have ectopic pregnancy that can be fatal.[11,12] Among infants born to infected mothers, 18-50% will develop ocular infections and 10-16% will contract chlamydial pneumonia.[13,14]

## PATHOPHYSIOLOGY

*C. trachomatis* is a coccoid, Gram-negative,

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obligate intracellular bacterium. The organism appears in two distinct forms, the elementary body (EB) and the reticulate body (RB). The EB, the infectious form of the agent, attaches to the host cell surface and is brought into the cell by endocytosis. Within the phagosome, the bacterium differentiates into metabolically active RB. Then the RB reproduces by binary fission. When the host cell is depleted of its adenosine triphosphate and essential amino acids, the newly formed RBs undergo a secondary metamorphosis and return to the EB form, thus completing the life cycle.

## DISEASE SPECTRUM

Antigenic determinates define 15 serovars that cause three major types of infection. Those are trachoma, oculogenital infections and lymphogranuloma venereum. The oculogenital infections are caused by serovars D through K. Apparently the bacterium does not infect squamous epithelium but has a preference for columnar epithelium. Therefore, the cervix and various other areas containing columnar epithelium are the targets of the organism.

### Infection in men

Urethritis is by far the most common clinical manifestation in men. It may manifest as non-gonococcal urethritis (NGU) or post-gonorrheal urethritis (PGU). Though chlamydial infection in male urethra does not result in large number of complications, this group may represent a large reservoir for infection in women. Males may also be asymptomatic without urethral discharge. Rarely, chlamydial urethritis can progress to prostatitis and epididymitis and is associated with male infertility. *C. trachomatis* is the most common cause of epididymitis among men younger than 35 years of age, leading to significant morbidity.[6] The organism is also associated with 50% of cases of Reiter's syndrome that is not associated with gastrointestinal pathogens.[15]

### Clinical manifestations and complications among women

Up to 70% of the infection can be asymptommatic. When symptoms occur, they include uncharacteristic or blood stained discharge and urethral symptoms such as dysuria and frequency. Though endocervix is the most common infected site in female, urethrits is not that uncommon. Studies showed that 15-25% of female sex partners of chlamydia-infected men have positive chlamydial urethral cultures. If urethral culture was done in addition to the endocervical culture, the yield of culture-positive women was increased by as much as 28%.[16] Therefore, one should always bear in mind the possibility of chlamydial infection in case of unexplained pyuria or culture-negative 'cystitis' in sexually active women, chlamydial urethritis can occur alone in the absence of endocervical infection.

#### *Lower Genital Tract Infections*

Endocervicitis is the most common presentation of chlamydial infection. The overt signs of the infection include the presence of mucopurulent discharge or a friable, easily bleeding cervical ectopy. A Gram stained smear of the cervical secretions may also be helpful. Identification of 10 or more polymorphonuclear cells per 1,000 microscopic field correlates strongly with chlamydial endocervical infection. However, up to 5% of chlamydia culture-positive cervicitis cases have a macroscopically clear cervical secretion.[17,18]

#### *Upper Genital Tract Infections*

If the lower genitourinary tract infection is left untreated, it can persist for months and being transmitted to others. During this period, the infection can ascend the endometrium and fallopian tubes causing lower abdominal pain and menstrual abnormalities. Chlamydia, alone or with other microorganisms, has been isolated from 5-50% of women seeking care for symptoms of PID.[1] PID is particularly likely if the cervical barrier has been breached, e.g. following insertion of an intrauterine device (IUD) or during termination of pregnancy.

The clinical course of chlamydial PID is less dramatic than that of gonococcal PID because of the absence of classic acute inflammatory response. Studies in women with tubal infertility indicate that up to 50% of instances of chlamydial tubal infections can be asymptomatic and less than 40% of patients have a febrile illness.[19] What detrimental is that these 'silent' episodes of salpingitis may cause significant and permanent scarring leading to subsequent tubal occlusion, ectopic pregnancy, chronic pelvic pain and infertility. No wonder why prevention and early detection of the infection with prompt treatment is so important to minimize these serious sequelae.

## DIAGNOSIS

After the introduction of the nonculture tests in 1980s, a more broad-based testing is possible because of the less stringent demands in handling of the specimens. They are easier to perform and less expensive than tissue culture (TC) which is considered as the traditional 'gold standard' for *C. trachomatis* testing. The expanded use of the nonculture tests is a cornerstone of chlamydia prevention strategies. However, the recent development and application of molecular techniques such as the polymerase chain reaction (PCR) and the ligase chain reaction (LCR) has led to a reappraisal to the sensitivity and specificity of the nonculture tests and TC.

### Laboratory techniques

· ***Tissue culture (TC)***

In TC, organisms from each of three chlamydia species (*C. trachomatis, C. pneumoniae, C. psittaci*) grow and produce intacytoplasmic inclusions. The direct visualization of these inclusions stained by the species-specific anti-major outer membrane protein (MOMP) antibody contributes to the specificity of the TC. Culture sensitivity has ranged from 33-86% and the specificity approaches 100%.[2] It can be used for endocervical, urethral, eye, nasopharyngeal and rectal specimens.

· ***Nonculture Chlamydia tests***

These antigen detection tests have been popular since their production because of less stringent demands in transportation and the technique is less laborious or time consuming. The main categories are direct fluorescent antibody (DFA) tests and enzyme immunoassay (EIA) tests. For DFA, the endocervical specimen is stained with fluorescent monoclonal antibody that binds to the chlamydia elementary bodies (EB). Stained EB are then identified by fluorescence microscopy. EIA tests detect chlamydia lipopolysacccharide (LPS) with a monoclonal or polyclonal antibody that has been labeled with an enzyme. The enzyme converts a colorless substrate into a colored product. Cross-reaction of the antibody with other microorganisms leads to false-positive results. Moreover, the LPS-based tests are not species-specific. Studies showed the overall sensitivity between 60-85% and the specificity between 90-99%.[2] The predictive values of positive and negative tests vary with the prevalence of genital chlamydial infection in the population studied. Therefore, these tests are more useful in studying high prevalence (>5%) population; in low-prevalence settings (<5%), a positive test needs to be confirmed by cost-increasing confirmatory tests.[1]

· ***Nucleic acid amplification tests (NAAT)***

The more popularly used target amplification techniques are ligase chain reaction (LCR) and polymerase chain reaction (PCR). For PCR, the target strands are hybridized with oligonucleotide primers. Then the primers are extended on the DNA template by a DNA polymerase to generate a new double-stranded DNA. After repeated cycles, million copies of the target DNA can be produced. LCR is based on target-dependent ligation of oligonucleotide probes. The ligation product, which mimics one strand of the original target sequence, can serve as a template for another cycle of ligation. The amplified DNA produced by PCR or LCR can therefore be easily detected by EIA. Both tests can offer a sensitivity of at least 95%. In multicentre trials, it was shown that the NAAT could increase the number of infections detected (i.e., sensitivity) by 10-20% where culture systems were optimal to as much as 80% or more when compared with nonculture tests.[20-22] False-positive can happen when there is carryover contamination of pre-amplified specimens by the post-amplified product during processing. If this is avoided, the specificity of these tests can reach 99.8%. Moreover, the NAAT have a profound advantage as being noninvasive since the first void urine can be used for analysis. In addition, the use of vaginal and vulval specimens for women appears to be equally effective when compared with cervical specimens.[23]

The following table gives a summary of various tests:

| Test | Sensitivity(%) | Specificity(%) | Advantages | Disadvantages |
|---|---|---|---|---|
| Tissue culture(TC) | 65-85 | 100 | Definitive | Quality of specimen; Transport; Cell culture facilities; Variations in method |
| Immuno-fluorescence (DFA) | 80-85 | >95 | Non-viable organisms; Quality of specimen can be checked; Sensitivity; Speed with small numbers | High technical expertise; Good quality equipment; Subjectivity; Tedious |
| Enzyme Immunoassay (EIA) | 60-80 | 99 (confirmed) >90 (unconfirmed) | Non-viable organisms; Less subjective than DFA; Can be mechanized; Batch processing | Quality of specimen; Low antigen concentration; Fair sensitivity; Fair specificity (needs confirmatory test) |
| DNA probe | 75-85 | >99 | Non-viable organisms; Specificity; Batch processing | Quality of specimen; Fair sensitivity; Radioactivity (not all techniques) |
| LCR/PCR | >95 | >99 | Non-viable organisms; Batch processing; Machine read; Sensitivity and Specificity; Urine specimen | Contamination; Cost |

## TREATMENT

The recommended treatment regimens for uncomplicated urethral, endocervical, or rectal chlamydial infections among adults are listed below.[24]

- Doxycycline 100 mg orally 2 times a day for 7 days; or
- Azithromycin 1 gm orally in a single dose

Alternative treatment regimens

- Erythromycin base 500 mg orally 4 times a day for 7 days or 250 mg 4 times a day for 2 weeks; or
- Ofloxacin 200 mg orally 2 times a day for 7 days
- Tetracycline 500 mg orally 4 times a day for 7 days
- Amoxicillin 500 mg orally 3 times a day for 7 days

During pregnancy, the drugs safe to be used are erythromycin and amoxycillin. The safety and efficacy of azithromycin among pregnant or lactating women have not been established. Treatment failures, indicated by positive cultures 7-14 days after therapy, is uncommon after a successful completion of >7 day regimen of tetracycline or doxycycline; or single dose of azithromycin. Therefore, retest for chlamydia after completing treatment with doxycycline, azithromycin or ofloxacin is not necessary unless symptoms persist or re-infection is suspected. Re-test may be considered 3 weeks after treatment with erythromycin or amoxicillin. If re-testing is done <3 weeks after treatment, false-negative results may occur because of small number of surviving chlamydial organisms. Moreover, nonculture tests conducted at <3 weeks after therapy may sometimes be false-positive because of the continued excretion of dead organisms.[1]

Studies showed that 30-54% of adolescent girls experience a persistent or recurrent infection within 2-5 years after their first infection,[25] indicating high chance of re-infection among them. Therefore, regular screening at time intervals after therapy may be necessary especially in high-risk groups.

### Presumptive diagnosis and treatment

Co-infection of *C. trachomatis* in gonorrhea is reported to be high (25-50%) in women.[1] Therefore, under a presumptive diagnosis of chlamydial infection in patients with gonorrhea, treatment regimen to include antibiotic for chlamydia is justified.

### Management of sex partners

Patients should be instructed to refer their sex partners for evaluation and treatment since the latter can remain as source of re-infection to the index patients if left untreated. In most of the studies about the correlates of chlamydial infection in sexual partnerships, usually more than 50% of sex partners are detected to

be chlamydia-infected. According to the 1993 CDC STD treatment guidelines, for women with chlamydial infections and for asymptomatically infected men, treatment should be given to all sex partners with whom patients have ongoing sexual relations and all other partners with whom patients have had sexual exposures within 60 days before the date of the patient examination/test. For males with symptomatic chlamydial infection, the 30-day period is sufficient to detect person(s) who probably transmitted the infection to the index patient, as well as recent sex partners who may have been exposed to the infection by the patient.[1] Patients should be instructed to abstain from sexual intercourse until patient and sex partners have completed therapy and without symptoms or signs.

## STRATEGIES OF INTERVENTION

The major goals of intervention are prevention of chlamydial infection and early detection of the infected individuals to prevent sequelae and further spread of the infection.

### Community-based strategies

Chlamydial infection is highest among the adolescents and young adults. It is because the primary target cells for *C. trachomatis* infections are columnar epithelial cells. Physiologically, the increased exposure of cervical columnar epithelium in adolescent females is believed to increase the chance of getting the infection when exposed to the organism. Behaviorally, adolescence is characterized by low perceived vulnerability to danger and risk-taking behaviors. Therefore, they tend not to use barrier contraception. Unfortunately, young females are the one who will be more likely to suffer from long-term morbidity resulting from the complications of infection. Therefore, more efforts should be paid to increase the public awareness of the infection and its consequences. Safe sexual practice and the use of condom should always be emphasized to minimize the risk of transmission of the disease.

### Health-care provider strategies

One may realize that majority of patients are taken care by all kinds of health-care providers including the family physicians, obstetricians-gynecologists and pediatricians. Therefore, they should be able to recognize chlamydial illness and its complications, offer screening appropriately, arrange treatment for sex partners, and refer the risk-exposed individuals for complete STD screening. The following criteria can help to identify women who should be tested for chlamydia:

- Women with mucopurulent cervicitis
- Sexually active women <20 years of age
- Women 20-24 years of age who meet either of the following criteria, or women >24 years of age who meet both criteria: inconsistent use of barrier contraception, or new or more than one sex partner during the last three months.[1]

For asymptomatic pregnant women but risk-exposed, chlamydial test is recommended to be done during the third trimester, so that treatment, if needed, will be completed before delivery to prevent perinatal transmission and postpartum PID. Evidence for adverse effects of chlamydial infection during pregnancy is minimal. Hence, if screening is done only in the first trimester, a longer period exists for infection before delivery.

***Learning points:***

***Chlamydia trachomatis is the leading pathogen of sexually transmitted diseases. If left untreated, serious sequelae such as infertility and ectopic pregnancy can occur.***

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## Answers to Dermato-venereological Quiz on page 141

### Answer (Question 1)

1. The diagnosis is hypertrichosis lanuginosa acquisita.

2. It is usually secondary to malignant tumors of the gastrointestinal tract, lung, pancreas, lymphoma, and uterus. It is characterized, in its extreme, by the rapid growth of fine, downlike hair all over the body, occasionally associated with glossitis and loss of taste. Successful treatment of the malignancy has been associated with remission of the hypertichosis.

3. The other possible causes are anorexia nervosa and drugs such as minoxidil, phenytoin, cyclosporine, and steroids. This patient had underlying carcinoma of pancreas.

### Answer (Question 2)

1. The diagnosis is xanthoma disseminatum.

2. The histopathology may show a mixture of foamy cells, histiocytes, and Touton giant cells. The proliferating cells are S-100 and CD1a negative.

3. The cause of the raised serum sodium level is due to meningeal infiltration at the base of the brain by the xanthoma causing diabetes insipidus.