A Review of Genital Chlamydial Infections

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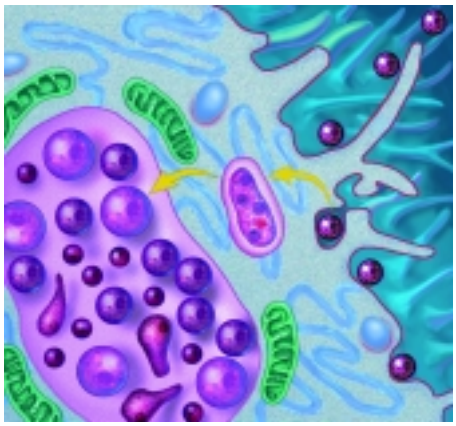
Chlamydiae are obligate intracellular parasites containing both DNA and RNA.[1] Three species of the genus *Chlamydia* infect humans: *Chlamydia psittaci*, *Chlamydia trachomatis*, and *Chlamydia pneumoniae*. Of these three species, *C. trachomatis* is predominantly a human pathogen and is a major cause of sexually transmitted diseases (STDs).



Genital infections caused by *C. trachomatis* are the most common bacterial STDs in the United States. More than 4 million cases occur each year[2] and the annual costs have been estimated to exceed $2.4 billion.[3,4] According to the Centers for Disease Control and Prevention[2] (CDC), age is the sociodemographic factor most strongly associated with *C. trachomatis*. The prevalence of chlamydial infection in sexually active adolescent females is greater than 10%. Other factors associated with higher prevalence include living in an urban area, black race, and lower socioeconomic status. The overall prevalence of chlamydial infection in the United States, regardless of region, is at least 5%.[2]

Infection by *C. trachomatis* is insidious because symptoms are absent in many infected individuals, especially men. Asymptomatic carriers of *C. trachomatis* are common, contribute to the widespread prevalence of chlamydia, and are at risk for developing both acute disease and long-term sequelae.

This article presents the clinical manifestations, diagnosis, and treatment of chlamydial infection. Pelvic inflammatory disease (PID) is also discussed.

CLINICAL MANIFESTATIONS

Specific Patient Populations

Women. Women are exposed to chlamydial infection through sexual intercourse with an infected partner. The cervix, urethra, or rectum may become infected, although many women with chlamydia are initially asymptomatic. Initial symptoms may include vaginal discharge or dysuria. Physical examination findings include erythema of the cervix and/or mucopurulent cervical discharge; however, these signs are absent in many cases. The upper genital tract, including the endometrium and fallopian tubes, may become involved. At least 20% to 40% of untreated cervical chlamydial infections ascend to the upper genital tract.[5] The risk of ascending infection is increased by douching.[6] Symptoms of upper genital tract infection include abdominal pain, fever, and menstrual irregularities. *C. trachamatis* is also an important etiologic organism for PID, as discussed later in this article.

Infants. *C. trachomatis* is the most common cause of neonatal conjunctivitis and one of the most common etiologies for pneumonia in the newborn.[2] Perinatal transmission of *C. trachomatis* is efficient. Nearly two thirds of infants born vaginally to infected mothers develop chlamydial infection.[7,8] Ocular prophylaxis at birth with silver nitrate or erythromycin ointment prevents gonorrheal infection but not *C. trachomatis* infection.[9] Screening of pregnant women prenatally may help to reduce the incidence of *C. trachomatis* infection in neonates.

Men. Many men with *C. trachomatis* infection are asymptomatic, thus facilitating transmission to sexual partners. Urethritis is the most common manifestation of chlamydial infection in heterosexual men.[2] Symptoms may also include penile discharge or dysuria. In men who engage in anal intercourse, the rectum is a frequent site of infection.[2] Epididymitis is usually caused by *C. trachomatis* in men younger than age 35 years. Men with epididymitis typically present with unilateral scrotal pain, fever, and epididymal tenderness or swelling.[1]

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Table 1. Treatment of Pelvic Inflammatory Disease

Outpatient therapy

Regimen A

Ofloxacin (400 mg) orally twice daily for 14 days plus metronidazole (500 mg) orally twice daily for 14 days

Regimen B

Ceftriaxone (250 mg) once intramuscularly plus doxycycline (100 mg) orally twice daily for 14 days

–OR–

Cefoxitin (2 g) once intramuscularly plus probenecid (1g) once orally plus doxycycline (100 mg) orally twice daily for 14 days

–OR–

Another parenteral third-generation cephalosporin (eg, ceftizoxime or cefotaxime) plus doxycycline (100 mg) orally twice daily for 14 days

Inpatient therapy

Regimen A

Cefotetan (2 g) intravenously every 12 hrs plus either intravenous or oral doxycycline (100 mg) every 12 hrs

–OR–

Cefoxitin (2 g) intravenously every 12 hrs plus either intravenous or oral doxycycline (100 mg) every 12 hrs

Regimen B

Clindamycin (900 mg) intravenously every 8 hrs plus gentamicin intravenously (loading dose, 2 mg/kg followed by 1.5 mg/kg every 8 hrs, OR once-daily dosing, 5 mg/kg)

Adapted with permission from Centers for Disease Control and Prevention: 1998 guidelines for treatment of sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep* 1998;47:1–111.

Associated Disorders

Reiter's syndrome. Primarily occurring among men, Reiter's syndrome is the constellation of urethritis, conjunctivitis, and reactive arthritis. More than 80% of individuals with Reiter's syndrome have the HLA-B27 phenotype. The pathogenesis of this syndrome is uncertain but may be linked to a genetic predisposition to develop a hyperactive immune response that produces inflammation in certain target organs.[1]

Fitz-Hugh–Curtis syndrome. Fitz-Hugh–Curtis syndrome is the result of a pelvic infection in women that progresses to perihepatitis and development of perihepatic adhesions. This syndrome occurs in 5% to 10% of women with acute PID. *Neisseria gonorrhoeae* or *C. trachomatis* may be the etiologic organisms involved.[10]

Pelvic inflammatory disease. *C. trachomatis* is an important etiologic organism for PID. PID represents an infection of any or all of the female's upper genital tract structures including the endometrium, myometrium, tubes, ovaries, and parametrium. Up to 50% of female patients treated for PID have evidence of *C. trachomatis* infection.[2] Approximately 10% to 40% of women with chlamydial infection of the upper genital tract develop PID.[5] However, women infected with *C. trachomatis* who use oral contraceptives appear less likely to develop PID compared with infected women who do not use oral contraceptives.[11]

Clinical presentation. The clinical presentation of PID varies widely. Abscesses may form in the adnexa. Symptoms include pelvic pain, fever, irregular vaginal bleeding, and vaginal discharge. Physical findings include cervical motion tenderness, adnexal tenderness or mass, and peritoneal signs (eg, rebound tenderness, guarding, abdominal rigidity). Leukocytosis may be present and the erythrocyte sedimentation rate or C-reactive protein level may be elevated.[10]

Diagnosis. Definitive diagnosis of PID is possible through laparoscopy. However, laparoscopy is not frequently performed because of the invasive nature and expense of the test. Diagnosis is based on clinical grounds and usually confirmed by response to treatment.[10] Compared with laparoscopy, diagnosis based on clinical criteria has a positive predictive value of 65% to 90%.[9] PID can be confirmed definitively by the presence of endometritis on endometrial biopsy, demonstration of tubo-ovarian abscesses by imaging techniques, or by laparoscopic confirmation as previously mentioned.[9]

Treatment. The CDC recommendations for treatment of PID are listed in **Table 1**. Broad-spectrum treatment is indicated because PID is often the result of a multiorganism infection. However, treatment of PID must include coverage for *C. trachomatis* regardless of whether the culture is positive for the organism.

Inpatient treatment for PID is reserved for patients who are nulliparous or pregnant, or patients with tubo-ovarian abscess, gastrointestinal symptoms, peritonitis in upper quadrants, history of a recent gynecologic operative or diagnostic procedure, or concurrent HIV infection.[2] Adolescent patients, patients with an intrauterine device, patients with uncertain diagnosis, or patients with an inadequate response to outpatient therapy are also candidates for inpatient treatment.[2]

The CDC recommends that empiric treatment of PID be initiated in sexually active young women if no other etiology is found and the following three criteria are present: 1) lower abdominal tenderness, 2) adnexal tenderness, and 3) cervical motion tenderness. Empiric treatment is recommended to avoid delay in treatment of PID and possible development of long-term sequelae.

Outcomes. Long-term sequelae of PID include 1) infertility, 2) an increased risk for ectopic pregnancy, and 3) chronic pelvic pain. Most of these sequelae are the result of persistent and/or recurrent fallopian tubal infection with resultant tubal damage.[5] Studies have demonstrated persistent *C. trachomatis* in the fallopian tubes of women despite treatment with appropriate antibiotics.[12] The risk of ectopic pregnancy after chlamydial PID infection increases tenfold.[5] The rate of infertility because of tubal factors in women with a history of PID caused by chlamydia ranges from 8% to 40%.[5] As many as 18% of women with chlamydial PID develop chronic pelvic pain.[13] Recurrent PID occurs in approximately 25% of women with a history of PID.[10]

DIAGNOSIS AND SCREENING

In the past, the gold standard for *C. trachomatis* detection was cell culture.[5] However, cell culture is difficult and time consuming. Epithelial cells from the urethra or cervix must be collected and placed in special media. The specimen must then be plated within 24 hours and incubated. Diagnostic tests have been developed to overcome the difficulties inherent in the cell culture process. **Table 2** demonstrates nonculture tests now available for detection of *C. trachomatis*.

Table 2. Comparative Performance of Select Diagnostic Tests for Detection of *Chlamydia trachomatis*

Test	Sensitivity, %	Specificity, %	Detection Level*
Enzyme immunoassay	40–60	99.5	1000–10,000
Nonamplified genetic probe	40–65	99	1000–10,000
Direct fluorescent antibody	50–80	99.8	50–1000
Cell culture	50–90	99.9	10–100
Ligase chain reaction			
Cervix	81–100	99.7	1–10
Female urine	69–96	99.7	1–10
Male urine	90–96	99.7	1–10
Polymerase chain reaction			
Cervix	60–92	99.6	1–10
Female urine	82–93	99.6	1–10
Male urine	87–100	99.6	1–10

*Elementary bodies.

Adapted with permission from Marrazzo JM, Stamm WE: New approaches to the diagnosis, treatment, and prevention of chlamydial infection. *Curr Clin Top Infect Dis* 1998;18:45.

Direct Fluorescent Antibody and Enzyme Immunoassay

The most widely used assays are the direct fluorescent antibody (DFA) and enzyme immunoassay (EIA) tests. In cervical specimens, test sensitivity ranges from 60% to 85%. Test results are usually available within 1 to 2 days.[5] DFA became popular in the late 1980s and is based on staining smears with monoclonal antibodies specific for the chlamydial elementary body. The test's sensitivity is largely dependent on the observer's ability to interpret the slide. Thus, more experienced observers/technicians are required to obtain optimal results. EIAs are much easier to perform than DFA tests; however, EIAs are less sensitive. Sensitivity of EIAs typically ranges from 60% to 70%, but can be improved by combined screening with DFA.[14] Rapid antigen tests have been developed that can be performed in an office setting while the patient waits. These tests are usually EIA-based tests that have a high false-negative rate (approximately 50%); thus, their role in screening and diagnosis is limited.[14]

Other Tests

Detection of chlamydial DNA by specific probes became popular in the 1990s. The test, called the *Probe Assay Chemiluminescence Enhanced (PACE-2)* (Gen Probe [San Diego, CA]) is as sensitive as a culture and is comparable to EIA in sensitivity.[14] The test is easy to perform in large volumes and the interpretation of test results is straightforward. However, the PACE-2 test does not amplify DNA, which is an advantage of the polymerase chain reaction (PCR) and ligase chain reaction (LCR) methods. PCR and LCR have high sensitivity and specificity and may become the diagnostic tests of choice for *C. trachomatis* infections.

Recently, Gen Probe has developed a new RNA amplification method for detection of *C. trachomatis*, called *AMP-CT*. In this method, ribosomal RNA is amplified without a thermal cycler, which is technically easier to perform than the PCR method. Transportation and storage of the specimens is less critical in these nucleic acid amplification tests than in culture-based methods. The amplification method also has a sensitivity advantage compared with culture methods, which is particularly important when screening patients with low numbers of chlamydia particles (eg, asymptomatic individuals).[15]

Sample Collection for Testing

Traditional sampling for culture-based testing requires swabs of the urethra or endocervix. The new

Table 3. Treatment of *Chlamydia trachomatis* Infections in Adolescent and Adult Patients

Recommended regimens
Azithromycin (1 g) orally in a single dose
–OR–
Doxycycline (100 mg) orally twice daily for 7 days
Alternative regimens
Erythromycin base (500 mg) orally four times daily for 7 days
–OR–
Erythromycin ethylsuccinate (800 mg) orally four times daily for 7 days
–OR–
Ofloxacin (300 mg) orally twice daily for 7 days

Adapted with permission from Centers for Disease Control and Prevention: 1998 guidelines for treatment of sexually transmitted diseases. *MMWR Morb Mortal Wkly Rep* 1998;47:1–111.

nucleic acid amplification techniques allow for detection of *C. trachomatis* in noninvasive samples such as first-void urine (FVU) and vulvar swabs. These new techniques may allow for widespread self-screening for *C. trachomatis* infection and better patient acceptance.[15]

Screening

Because many women and most men with *C. trachomatis* infection are asymptomatic, screening is vital in order to reduce propagation of the disease. Annual testing is recommended for women at high risk for chlamydial infection. According to the CDC, the following patient populations should be screened for chlamydial infection:[2]

- Sexually active female adolescents
- Women undergoing induced abortion
- Women attending STD clinics
- Women with mucopurulent cervicitis
- Women with new or multiple sexual partners within 3 months of presentation
- Women who use barrier contraception inconsistently
- Women who are or have been incarcerated

Partners of infected women should be treated to avoid reinfection and reduce the spread of infection.[2]

Although several studies have demonstrated the value of screening for chlamydia, widespread screening is not currently practiced in the United States. Genc et al[16] found that, if the prevalence of *C. trachomatis* is at least 6%, PCR screening of asymptomatic women from an endocervical specimen is cost effective. Scholes et al[17] found that screening women at high risk for chlamydial infection followed by prompt treatment for infected patients reduced the incidence of PID. Screening for *C. trachomatis* in asymptomatic high-risk women thus reduces the incidence of chlamydial infection and may reduce the risk of developing long-term sequelae.

Screening in asymptomatic men is less well studied. One study demonstrated that FVU samples from men were as accurate for diagnosing *C. trachomatis* as urethral swabs.[18] FVU sampling is noninvasive and allows for self-testing at home. Gunn et al[19] tested 1860 teenage males with urine samples using PCR-based techniques, which was found to be a viable alternative to traditional swab-based testing. In a randomized study, Ostergard et al[20] demonstrated that the efficacy of home sampling was significantly greater than office-based sampling. More than 90% of teenagers gave home urine specimens versus less than 10% of patients in the office-based control group.[20]

Sexual partners. Sexual partners of all patients diagnosed with *C. trachomatis* infections should be evaluated, tested, and treated if they have had sexual contact with the patient within 60 days of symptom onset or diagnosis. If the patient has had no sexual contact within 60 days of diagnosis, the most recent sexual partner should be treated. Abstinence is recommended until the partner has been treated.[9] Referral of the partner to her or his own physician is usually the best way to accomplish testing and treatment, although practitioners may treat both partners at the same time. In either case, the treatment of partners should be simultaneous to help avoid reinfection.

TREATMENT

Antibiotics to treat *C. trachomatis* infections must have good cellular penetration because the actively dividing organisms are intracellular.[5] *C. trachomatis* has a long life cycle (48 to 72 hr); thus, prolonged treatment with a drug with a long half-life is necessary. Antimicrobial resistance has not yet been a clinical problem.[5] Empiric treatment (ie, before confirmatory test results are available) for *C. trachomatis* infection is recommended for patients with gonococcal infections, men with nongonococcal urethritis, and men younger than age 35 years with epidydimitis.[5]

Recommended Therapy

Suggested treatment regimens for *C. trachomatis* infections from the CDC are listed in **Table 3**. Doxycycline

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(from page 30)

has been considered as the main treatment for patients who are not pregnant. Recently, ofloxacin and azithromycin have emerged as alternative treatments. All regimens are equivalent in effectiveness. However, azithromycin provides the advantage of a single, one-time dose regimen, which improves patient compliance. Although the azithromycin regimen costs more than the doxycycline regimen, studies have demonstrated that azithromycin is more cost effective because of the increased patient compliance with the single dose.[21,22] Augenbraun et al[23] found that 24% of patients in an STD clinic were noncompliant with the 7-day doxycycline course of treatment for *C. trachomatis* infection. To prevent transmission of unresolved infection to sexual partners, sexual abstinence is recommended for 7 days with the single-dose azithromycin treatment and throughout treatment with the 7-day regimens.[5]

Second-Line Agents

Amoxicillin, erythromycin, and sulfa drugs have been used as second-line agents for the treatment of *C. trachomatis* infections. These drugs are less effective (ie, 60% to 80% effective) than the CDC-recommended agents.[5] However, the second-line agents have often been prescribed for patients who are pregnant because the first-line treatments doxycycline and ofloxacin are both contraindicated in pregnant patients. Azithromycin may be used in pregnant patients; however, data on the effectiveness of the single-dose regimen in these patients are not yet available.[5]

Test of Cure

Test of cure, although not generally recommended in the routine follow-up of patients treated for *C. trachomatis* infection, is indicated in patients who are pregnant and in patients who are treated with second-line agents because treatment failures are more common in these groups. In both of these patient groups, test of cure should be performed no earlier than 3 weeks after completion of treatment. In addition, re-screening adolescent patients may also be useful because of the high risk of reinfection in this population.[9]

SUMMARY

C. trachomatis infections are widespread and cause a range of diseases and syndromes, including PID. PID is usually diagnosed on clinical grounds, and treatment of PID involves the use of broad-spectrum antibiotics. Chlamydial infections tend to cause higher morbidity among women; men tend to remain asymptomatic. Screening of asymptomatic individuals is important to avoid transmission to sexual partners and to avoid long-term sequelae. New screening techniques may lead to earlier treatment and prevention of transmission. New antibiotic regimens, although initially more expensive, improve patient compliance. **HP**

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