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Chlamydial infections in women

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Abstract

Chlamydia trachomatis (Ct) is a Gram-negative bacterium with an obligatory intracellular life cycle. Tropism manifests through columnar epithelia in the uterine cervix, rectum, lungs, and eyes. The literature review of the Medline database identified 3,458 papers. The WHO estimates that over 100 million new cases of infection by Ct occur worldwide annually, with an increase of 4.1% since the last global evaluation conducted in 2006. *Chlamydia trachomatis* is the most frequent sexually transmissible bacterium in the United States with a yearly incidence of more than one million reported cases.

Approximately 50 to 75% of infected women show no symptoms of the infection or appear to be mucopurulent cervicitis. Pain caused by cervical motion or evaluation of the accessories in response to a bimanual exam suggests the infection has moved on to the upper genital tract leading to endometritis, salpingitis and peritonitis and its consequences: pelvic pain, infertility, ectopic pregnancy. *Chlamydia trachomatis* may also be the etiologic agent of bacterial urethritis, in which case, despite the patient's report of dysuria, the urine culture is negative for the usual urinary pathogens. Since bacteria favor columnar epithelia, the Skene and the Bartholin vestibular glands may also be a site of infection and attendant symptoms.

The nucleic acid amplification test is the most recommended for its higher sensitivity and specificity and is currently the gold standard for diagnosis. The antibiotics for the treatment should be chosen for their intracellular penetration ability and should have a half-life of 36 to 48 hours to cover the bacterium's life cycle. Azithromycin is excellent at intracellular penetration, has a half-life of 5 to 7 days, and can be administered in a single dose; it may also be given to pregnant women. A recent meta-analysis showed a small increase (3%) of better outcome in the use of doxycycline against azithromycin in the treatment of urogenital infection.

Summary of recommendations

1. The nucleic acid amplification test (NAAT) is most recommended for its high sensitivity and specificity and is currently the gold standard for diagnosis.
2. Collection of specimens from the vagina for a culture test appears to be as sensitive as from the endocervix.
3. Azithromycin is excellent at intracellular penetration, has a half-life of 5 to 7 days, and can be administered in a single dose. Another advantage is that it can be given to pregnant women.
4. The following are alternative regimens: doxycycline twice daily for seven days; oral erythromycin, 500 mg four times daily for 7 days; oral erythromycin ethylsuccinate, 800 mg four times daily for 7 days; levofloxacin, 500 mg once daily for 7 days; or oral ofloxacin, 300 mg twice daily for 7 days.

1 Introduction

Chlamydia trachomatis (Ct) is a spherical or oval Gram-negative bacterium, and, contrary to other bacteria, has an obligatory intracellular life cycle. It has characteristics similar to those of viruses, such as size (0.2–1.3 microns), host cell dependence for energy production, intracellular life cycle, formation of cytoplasmic inclusions, and inability to grow in a synthetic culture medium. Tropism manifests through columnar epithelia in the uterine cervix, urethra, rectum, and as far away from the genital tract as the lungs and eyes [1], [2], [3]. According to its phylogenetic classification, Ct belongs to the *Chlamydiales* order, *Chlamydiaceae* family, *Chlamydia* genus, and *trachomatis* species. Nineteen different serotypes of the bacterium have already been described. The D to K serotypes (including Da, Ga, and Ia) are

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related to urogenital infections; the A, B, Ba, and C serotypes cause ocular trachoma, and the L1, L2, and L3 serotypes are sources of venereal lymphogranuloma [1]. *Chlamydia trachomatis* has a biphasic life cycle represented by elementary corpuscles (ECs) and reticular corpuscles (RCs). The ECs are characteristic of the infectious form, are metabolically inert, are responsible for epithelial cell invasion, and are found in the extracellular environment. The RCs are intracellular, larger, richer in RNA, and are the active, replicative, and noninfectious metabolic form of the bacterium, accounting for the chronicity and persistence of the disease [4].

The ECs attach themselves to the surface of the epithelial cell and are incorporated into the phagosome (inclusion vacuole), which migrates to the distal region of the Golgi apparatus, thereby remaining protected against the attack of lysosomes. Inside the phagosome, the ECs change into the metabolically active form, the RC. The process takes an average of 2 to 6 hours. The RCs thereafter start to replicate by binary division using the metabolites of the host cell, increasing the volume of the phagosome. Replication peaks between 18 and 24 hours [4]. Next, the RCs resume the shape of ECs, generating vacuoles inside the cytoplasm. When these have replaced almost all of the host cell's cytoplasm, the cell undergoes lysis, releasing infectious ECs into the extracellular environment, thus giving rise to a new infection cycle. This is one of the most differentiated replication mechanisms found in nature, making it easy for infection chronicity to set in. There is an exchange of material between the bacterium and the infected cell, hindering recognition by the host's immune system [5].

To ensure survival in the extracellular environment and to complete its reproductive cycle, Ct is able to inhibit apoptosis of the infected cells. How this happens is still fairly unclear. Nonetheless, the mechanism involves the production of factors by the bacterium which negatively regulate the cascade of events culminating in apoptosis [6].

2 Methods

The literature review was conducted using the primary Medline database and accessing the MeSH term "*Chlamydia* infections". Studies in Portuguese, English, Italian, French, and Spanish were included with no bars on year of publication. Only studies of the infection in women were considered for analysis. The search with these criteria yielded 3,458 papers. Screening them for topic relevance, based on evaluation of titles, abstracts, and the reading of the entire text, led to the selection of 36 articles for this review.

3 Epidemiology

The World Health Organization estimates a worldwide occurrence of over 100 million new cases of both sexes with infection by Ct annually and an increase of 4.1% since the last global evaluation, carried out in 2006 [7].

According to the Center for Disease Control and Prevention, Ct is the most frequently encountered sexually transmissible bacterium in the United States with more than one million reported cases yearly. Annual tracking is recommended by the United States Preventive Services Task Force for sexually active women up to 25 years of age and for women over 25 at risk for the infection (multiple sexual partners, partners with sexually transmitted diseases, or new partners). A recent report showed that prevalence among the 14- to 39-year old population was 1.7%. However, in the sexually active women aged 14 to 24 years, there was an overall prevalence of 4.7%. In black women from this group, prevalence rose to 13.5% [8]. A study conducted in Germany showed the infection prevailed among 2.2% of the female adolescents aged between 15 and 17 years and among 0.2% of the 16- and 17-year old male teenagers [9]. In Norway, prevalence ranged from 6.2% to 7.3% among youth of both sexes in the 15 to 20 age bracket. Redmond and collaborators carried out a meta-analysis of the studies of the prevalence of the infection in European developed countries, addressing both men and women under 26 years of age. Prevalence in women ranged from 3.0% to 5.3%, with an average of 3.6%, and in men from 2.4% to 7.3%, with an average of 3.5% [10].

Approximately 70 to 90% of *Chlamydia trachomatis* urogenital infections in women are asymptomatic [11].
A randomized clinical trial conducted by Oakeshott et al. [12] found that the relative risk of developing PID after 1 year of asymptomatic Ct infection without treatment was 6.6 (95% CI 2.8–15.5).
The authors suggested in the same article that the risk of progression to PID, ectopic pregnancy and tubal infertility after an episode of Ct infection would be 0.43%, 0.07% and 0.02%, respectively.
The ovarian tube abscess is a complication of approximately 0.8% of cases of PID and may require laparoscopic surgical treatment [13].
However, a recent Cochrane review concluded that there is moderate quality evidence that detection and

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treatment of *Chlamydia* infection can reduce the risk of PID in women at an individual level. There is an absence of randomized control trials about the effects of *Chlamydia* screening in pregnant women. The review emphasized the importance of future randomized controlled trials on *Chlamydia* screening and its effects in pregnancy [14].

4 Immunology

Chlamydia trachomatis has the ability to persist in the host, even after activation of the immune response, which involves interaction between the host and several antigens of the bacterial cell. There are two antigens connected with the diagnosis and pathogenesis of infection by Ct: lipopolysaccharide (LPS) and the antigen of the major outer membrane protein (MOMP). The LPS antigen is shared by all of the species of the microorganism and is more frequently found in the RC. It is responsible for the pathophysiological mediation of the bacterium. On the other hand, the MOMP antigens are species-specific and thus are used for serotyping and differentiating between the various serotypes. The antibodies produced against the MOMP are associated with the protective immune response [15].

The LPSs of the bacterium have a low potential for immune system activation, much lower than that of *Salmonella* (a 100-fold lower potential). The slow immunity development of the host may be due both to the low activation potential of the immune system and to the ability shown by Ct to regulate negatively major histocompatibility complex classes I and II, induced by interferon gamma [16].

Signals, derived from toll-like receptors (TLRs), are components of the innate immune system and are implicated in the pathogenesis of the infection. *Chlamydia trachomatis* has several cell wall and external membrane components which may be used as pathogen-associated molecular patterns, which are recognized by the TLRs. The TLRs 2 and 4 are the best known, as regards the innate immune response of Ct. The TLR 2 is involved in the recognition of the peptidoglycan (PGN) components of the bacterium. The LPS components and the heat shock proteins (HSPs), on the other hand, are binders for the TLR4. Both the TLR2 and the TLR4 are expressed in the female genital tract. The TLR2 is found mostly in the uterine tubes and in the cervix, whereas the TLR4 is predominant in the uterine tubes and the endometrium and weakly expressed in the ectocervix. Accounting for these differences are the different functions of the genital tract, such as protection against sexually transmissible diseases, which does not change the commensal vaginal flora, and the tolerance for semen with respect to embryo implantation. The binding of peptidoglycans, lipopolysaccharides, and heat shock proteins to the TLRs activates phagocytes and also stimulates the production of proinflammatory cytokines, such as TNF-alpha and IL-6. When the bacterium enters the cell, it is recognized by the nucleotide-binding oligomerization domain-like (NOD-like) receptors through the LPS and the PGN, thus initiating the immune response [17], [18].

The innate immunity cells produce defense factors, such as secretory leukocyte protease inhibitor, human beta-defensin 2, lisozyme, lactoferrin, etc. The immune cells, such as macrophages, neutrophils, and natural killers, produce soluble antimicrobials, chemokines, and proinflammatory cytokines in fighting against infection by Ct. Recruitment and activation of adaptive immunity (B and T cells) are instigated by the soluble antimicrobial factors of the epithelial and dendritic cells and by macrophages. In humoral immunity, the antibodies can prevent infection by Ct. In the genital tract, immunoglobulin G (IgG) is the most frequently encountered antibody. The antibodies from the plasma (IgG and IgA) inactivate the extracellular elementary bodies. In cell immunity, on the other hand, the CD4 T lymphocytes produce interferon-gamma (INF-gamma), which is connected with intracellular replication of Ct. The CD8 lymphocytes induce apoptosis in the infected cells [19].

Under usual conditions, months are necessary for immunity to develop against infection by Ct, probably due to the low virulence of the bacterium, its immunosuppressive properties, and its ability to survive outside of cells and persist in the intracellular medium. Spontaneous resolution of the infection in 82 women participating in a study was 54% in the first year, 82% in the second year, 91% in the third year, and 95% in the fourth year [16].

Several mechanisms have been proposed to explain the development of pathogenicity in the infection by Ct. Animal and human studies have shown that the proinflammatory cytokines produced to combat infection (TNF-alpha, IL-8, IL-1, and GM-CSF) are also responsible for tubal epithelial damage. The IL-1 is associated with the destruction of uterine tubes; the presence of IL-10 in cervical infections appears to be connected with infertility. The T cells of the immune system constitute the most important defense against Ct. Women with recurrent infections exhibit elevated INF-gamma levels; these high levels are associated with infertility. This became clear in a study in which each repeat episode of pelvic inflammatory disease doubled the risk of damage to the uterine tubes: 8% in the first episode; 19.5% in the second episode; and 40% in the cases of three or more infections [16].

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Another model reported in the pathogenesis of the infection by Ct involves the HSPs, which form a group of chaperones that take part in the correct folding of intracellular proteins. They are found in eukaryotic and prokaryotic organisms. Regulation by HSPs increases during cell exposure to temperature rises, oxidative stress, inflammation, etc. However, during the infection process, Ct also produces HSPs, particularly HSP60, which is highly immunogenic and highly homologous to human protein. Hence, the persistence of Ct and its continuous exposure to the antigen stimulate a specific cell response to the bacterium and simultaneously trigger a cross-reaction culminating in an autoimmune response; such events would determine the sequelae of the infection [20]. In humans, high antibody titers as a response to HSP60 are strongly associated with pelvic inflammatory disease, ectopic pregnancy, and infertility [4].

Recent studies showed the importance of the genetic polymorphisms of genes related to immune mediators as relevant factors in infection susceptibility. Such variations in immune response may influence the risk of infection persistence. Thus, in normal immune response, there is recognition of the pathogen by the TLRs and NODs, but in the genetic variations of the host, recognition is impaired, thereby allowing the infection to progress [16], [21].

When cervical infection by Ct is not adequately eliminated, it can ascend to the upper genital tract, causing pelvic inflammatory disease and attendant infertility. In pregnant women, the sequelae of the infection have been associated with increased risk of ectopic gestations, miscarriages, preterm births, low-birth-weight infants, premature rupture of the membranes, and puerperal and perinatal infections [2].

Another important aspect is that Ct has been included in the cofactors leading to the persistence of the infection by human papillomavirus (HPV) and, therefore, to the development of cervical carcinoma. Women infected by the bacterium exhibit a higher frequency of cytological changes, probably due to the production of enzymes with antiapoptotic action which facilitate the action of oncoproteins in cells infected by high-risk HPV. Thus, the infection by Ct seems to act synergistically with HPV, increasing the risk for squamous carcinoma and facilitating the effect of the virus in the neoplasm.

High cervical cancer rates in certain populations coincide with endemic or epidemic cervicitis. Inflammation as a response to chronic infection triggers the production of nonspecific oxidants which can harm DNA and potentially lead to the development of cancer. The association between inflammation and some types of cancer suggests that the former may be a universal risk factor for carcinogenesis [22], [23]. The hypothesis has been raised that Ct would aid HPV access to the basal layer of the epithelium when inducing chronic inflammation, hypertrophied cervix, and metaplasia, the latter a preferential HPV target [24]. These biological effects would increase the risk for changes in cervical cells and the persistence of infection by oncogenic types of the virus. It has also been proposed that the heat shock protein of Ct, HSP60, interferes in cell apoptosis and senescence, activating cell proliferation and increasing the opportunities for cell damage in cells infected by oncogenic HPV [21]. Additionally, Ct could encourage HPV persistence by lessening antigenic response to cells, thus inhibiting immune system cell production [25].

5 Clinical signs and symptoms and diagnosis

Infection by Ct is called ’the silent epidemic‘ since most of the female carriers, approximately 50 to 75%, display no symptoms of the infection. Such women serve as a bacterial reservoir, and they are transmitters who are susceptible themselves to the – occasionally serious – consequences of the infection.

When apparent, infection most often manifests as mucopurulent cervicitis, defined as the presence of mucopus in the endocervix and/or of 10 or more polymorphonuclear neutrophils per 100-fold magnified field. Specular examination of the cervix may show inflamed cervical ectropion, which bleeds upon touching. Cervicitis can be so extensive that it mimics vulvovaginitis. Pain caused by cervical motion or evaluation of the accessories in response to a bimanual exam, confirms a diagnosis of cervicitis, but also suggests, the infection has moved on to the upper genital tract (endometrium and uterine tubes). The clinical result is the pelvic inflammatory disease. *Chlamydia trachomatis* may also be the etiologic agent of bacterial urethritis, called ’urethral syndrome’, in which case, despite the patient’s report of dysuria, the urine culture is negative for the usual urinary pathogens. Since bacteria favor columnar epithelia, the Skene and the Bartholin vestibular glands may also be a site of infection and attendant signs and symptoms.

The diagnosis of infection by Ct may be reached by using a number of lab tests. The nucleic acid amplification test (NAAT) is most recommended for its high sensitivity and specificity and is currently

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deemed the gold standard for diagnosis. The serological tests are not indicated since the chronicity of the infection may invalidate the presence of an active infection. Culture is a good test, but not only is it difficult to transport and store, it is also an expensive technique, very often making it unusable [26].

The sensitivity and specificity of each of the techniques that may be used are displayed in the following table:

Table 1: Sensitivity and specificity of the detection tests for Chlamydia trachomatis, modified from Keegan MB et al. [27]

NAAT	Sensitivity	Specificity
Vaginal	97.2%	99.5%
Endocervical	91.7%	98.3%
Urine	91.7%	99.3%
DNA probe	68.8%	99.8%
Direct immunofluorescence	80–85%	99%
Immunoenzymatic assay	60–85%	99%
Cell culture	50–85%	100%

NAAT – nucleic acid amplification test

The NAAT with specimens collected from the vagina (vaginal swab) seems to yield results as sensitive as those obtained with specimens from the endocervix (endocervical swab). The possibility of checking for Ct in the residual sample volume of liquid-based cytology makes endocervical detection of Ct preferred in those cases in which women are to undergo cervical cancer screening. Urine testing is used quite frequently; however, it detects up to 10% fewer infections than vaginal or endocervical swabs [26], [27]. In women with PID samples collected from the Fallopian tubes may detect a higher rate of Ct infection than samples from other sites.

6 Treatment

To treat infection by Ct is to prevent potential complications and their sequelae, such as pelvic inflammatory disease, ectopic pregnancy, and vertical transmission, thereby preventing conjunctivitis and neonatal pneumonia. Besides, the bacterium can coexist with other genital infections, which makes it easy to transmit or acquire infection by HIV [28].

It is recommended that all infected people and their partners be treated. As the life cycle of Ct is biphasic and the infectious forms (elementary bodies) are metabolically inert and resistant, antibiotics should target the intracellular form. For this reason, the antibiotics should have good intracellular penetration in addition to a half-life of 36 to 48 hours for covering the life cycle of the bacterium. Azithromycin is excellent at intracellular penetration, has a half-life of 5 to 7 days, and can be administered in a single dose. Another advantage is that it can be given to pregnant women [21].

Doxycycline twice daily for seven days may be used as an alternative regimen. A recent meta-analysis showed a small increase (1.5%) in treatment efficacy in this use of doxycycline as compared to azithromycin for the treatment of urogenital infection [29].

The following treatments may also be administered as alternative regimens: oral erythromycin, 500 mg, four times daily for 7 days; oral erythromycin ethylsuccinate, 800 mg, four times daily for 7 days; levofloxacin, 500 mg, once daily for 7 days; or oral ofloxacin, 300 mg, twice daily for 7 days [30].

In pregnant women, the alternative recommendation is a single oral dose of 1 g of azithromycin or 500 mg of oral amoxicillin three times daily for 7 days [30].

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The prevention and control of *Chlamydia trachomatis* infections, as well other STIs, should be based on:

1. Risk assessment (behaviors that can increase the risk of infection); it is important that the health professional obtain a sexual history and assess the risk, with no judgmental attitudes, and deliver advise about risk reduction.
2. Identification of asymptomatic and symptomatic individuals with the disease. It is important to point out that any STI can represent a risk for other STIs.
3. Treatment and follow-up. Preventive counseling is also very important for adults and teenagers. Group-based strategies, when applied, are useful. Partner reduction (or abstinence) and the use of male and female condoms, correctly and consistently, are very important topics to be addressed.
4. Evaluation, treatment and counseling of sexual partners. Unfortunately, vaccination against *Chlamydia* is still being researched and is unavailable [31].

7 Further research

Chlamydia screening in young women may reduce pelvic inflammatory disease. Nucleic acid amplification tests are accurate for diagnosing *Chlamydia* in asymptomatic people using various types of specimens. Research is needed on the effectiveness of screening to reduce adverse health outcomes in specific population groups as pregnancy for example, effectiveness of different screening strategies, and its adverse effects are so important to develop guidelines.

8 Conclusions

Chlamydia trachomatis is a common sexually transmitted infection that is often difficult to detect due to the absence of defining symptoms in many women. Protocols to screen sexually active women for this infection by gene amplification tests and subsequent effective treatment offer the best opportunity to identify early stage infection, prevent serious and long lasting sequela, and reduce the rate of sexual transmission.

Conflict of interest

The authors declare no conflict of interest related to this chapter.

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