

# Current Understanding and Gaps in Knowledge of *Chlamydia trachomatis* Infection

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## Abstract

*Chlamydia trachomatis* is a bacterial infection that most frequently causes sexually transmitted infection in the world, therefore, it is considered a serious public health problem. The objective of this commentary is to describe in a condensed but sufficient manner what has been reported by researchers on the subject based on the documentary review available in digital repositories on aspects of the infection. The information obtained was grouped into 7 categories as a result of the analysis of relevant ideas. There are many aspects to be revealed in terms of pathogenesis, biology of the microbial agent, and treatment, hence the need to generate new knowledge in this regard and to carry out thematic consolidations such as the one presented here.

**Keywords:** *Chlamydia trachomatis*, Sexually transmitted infection, Public health, Infertility, Perinatal mortality

## Introduction

In developed and developing countries, *Chlamydia trachomatis* is the most important pathogen causing sexually transmitted infection [1], typically characterized by cervicitis and urethritis and causing sequelae as severe as pelvic inflammatory disease, infertility, ectopic pregnancy, repeated abortions, low birth weight, increased perinatal mortality and conjunctivitis and pneumonia in newborns [1,2]. For all the above, *C. trachomatis* infections are considered an important public health problem with high incidence and consequences on reproductive health and other organs and systems of the human body [3-7].

There is relevant information about this fearsome scourge, although incomplete, hence the need to recommend new research on the etiological agent, pathogenesis, immune response, diagnosis and treatment, and to offer writings that show in a condensed but sufficient way what has been

reported by researchers on the subject [8].

The objective of this article is to facilitate students, professionals, and health authorities in understanding the greatest number of variables on which action must be taken to control such a prevalent population health problem.

## Methodology

This article was based on the documentary review available in digital repositories on aspects of *C. trachomatis* infection, based on descriptors or keywords closely related to the topic. Repeated documents and those without clear or original conclusions were excluded. All original documents published from 1983 to August 2023 were included. The analysis of the ideas allowed them to be grouped into 7 categories (epidemiology of *C. trachomatis*, causal agent, pathogenesis, host immune response, diagnosis, treatment, and conclusions) for easy reading.

## Epidemiology of *C. trachomatis*

Throughout the world *C. trachomatis* is the bacterial infection that most frequently causes sexually transmitted infections (85 million cases are recorded annually in the world, with a global prevalence between 4.4 and 6.6%, with recurrent infections common and with high rates in developing countries despite under-reporting motivated primarily by the high cost of diagnostic tests). Mainly in sexually active young adults, with a higher prevalence in women in relation to men, and more frequent in the age period between 15 and 19 years, however, it is evident that the case mix differs between countries, therefore, it is recommended to adopt a rigorous registry [9-13].

Especially because the prevalence of *C. trachomatis* infection is different according to the different diagnostic methods used in the detection of this bacteria, for example, with direct procedures it has been possible to detect only between 0.7-2.3% of infected people, at this low sensitivity and specificity, it is added that at the time of bacterial diagnosis the patient is receiving antibiotics prescribed for conditions related to the genital sphere that mask the results obtained by direct diagnostic methods, hence serological diagnostic methods are preferred for population studies. The trend is towards an increase in the number of cases, except in those countries that have adopted national health programs for education, detection and treatment of *C. trachomatis*, and of course its complications [9,14-16].

It is prudent to highlight that with specific antibiotics, *C. trachomatis* infection heals easily with resolution in days or weeks, but since 70% of women and 50% of men do not show symptoms of genital infection (despite the high cure rate, recurrent and exacerbating infections occur), the health problem prevails or complicates its control, since they act as reservoirs capable of transmitting the infection to their sexual partners and because recurrence is common because the immune response against the pathogen is partially protective [8]. However, older women have an increased risk of infection by this bacteria if they are nulliparous, single, black, and have low income. Furthermore, in women, regardless of age, the large number of sexual partners, the beginning of a new sexual relationship, not using barrier methods such as contraceptives, and recurrent infections by *Neisseria gonorrhoeae* appear as risk factors for suffering from *C. trachomatis* infection [10,17-20].

Thus, in Western populations, *C. trachomatis* infection has been shown in epidemic proportions with severe consequences and negative impact for people and the community in general, specifically it affects fertility and the product of conception, and in what generally affects the socio-productive development of countries, due to the great economic and financial investment that the State must invest to treat the complications that this infection leaves in those affected (thus, more than 6 million blind people are

reported in the world), especially ocular pathologies, the risk of developing squamous cell cervical carcinoma [10,21].

## Causal Agent

*C. trachomatis* although phylogenetically distinct, is considered an obligate intracellular gram-negative bacteria (incapable of generating its own energy and dependent on the metabolism of the host cell) with a unique biphasic development cycle (the bacteria is found in two forms, one extracellular called elementary bodies and the intracellular body known as reticulate bodies), which belongs to the order *Chlamydiales*, family *Chlamydiaceae* and the genus *Chlamydia* (to which *C. muradum*, the pathogen of mice and hamsters, and *C. suis* that infects pigs also belong), They lack mitochondria, reproduce by binary fission, have DNA, RNA, and enzymes, and are capable of lysing the infected cell in 48 hours [22,23].

In their life cycle, the elementary bodies (osmotically stable and metabolically inactive) are considered the infecting forms, which after joining penetrate the cells by a still unknown mechanism, and remain internal in vacuoles, within these and after several transformations they differentiate in reticulated bodies (metabolically active). The reticular bodies are capable of dividing by binary fission approximately 18 hours after infection, the resulting reticular bodies are differentiated again into elementary bodies to be expelled from the cells, by exocytosis or cell lysis, 48 to 72 hours after infection [24].

The clinical diagnostic and epidemiological importance of the identification and classification of different isolates of *C. trachomatis* from the genital tract is recognized to establish test parameters of cure, as well as persistent infections versus reinfection and its role in complications, and in the association of strain-dependent virulence in relation to severe genital tract disease in women [10,25].

Currently, based on the functional variability of proteins (a product of evolutionary selection, for example the major chlamydial outer membrane protein [MOMP]), 18 *C. trachomatis* serotypes have been identified with unique attributes related to the severity of the disease and the prevalence of infection, of these D, E, F, G, H, I, J, and K are related to genital pathologies (disease-specific phenotypes). In addition, there are several candidates for virulence factors, among them are known: the polymorphic outer membrane autotransporter family of proteins, stress response proteins, the putative large cytotoxin, type three secretion effectors, and proteins or other regulatory factors produced by the cryptic plasmid. The incubation period of genital infection is 6-14 days, with a tendency to chronicity and generation of complications such as infertility, ectopic pregnancies and pathology of the perinatal sphere [10,26,27].

Serotypes A, B, Ba, and C have affinity for the connective epithelium, therefore, they can cause eye infections that

can progress to trachoma (the main cause of preventable blindness). Serotypes D-K, Da, Ia, and the genovariant Ja infect the genital epithelium and cause urogenital tract infections. Serotypes L1, L2, L2a, and L3 are capable of infecting the genital epithelium and also monocytes and causing a systemic disease known as lymphogranuloma venereum [21,27-29].

### Pathogenesis of *C. trachomatis* Infection

In women *C. trachomatis* is the cause of pelvic inflammatory disease, in men it is capable of infecting the accessory sexual glands and producing epididymitis, prostatitis, and urethritis (in the acute phase), and in both cases infertility. Furthermore, in men and women, already in the chronic or complicated phase, they generate glaucoma, endocarditis, coronary heart disease, chronic asthma, reactive arthritis, hepatitis and urethral syndrome, among others, which is why the pathogenic mechanisms involved in them are studied intensely and continuously the genesis of the aforementioned complications [16,30,31].

In this sense, several strategies have been proposed through which *C. trachomatis* leads to chronic infection, among them: asymptomatic infections by remaining silent that favor bacterial progression towards the most internal tissues (refers to the fact that the pathogenic agent possibly spreads found in an atypical, intracellular and metabolically less active state that is difficult to resolve not only by the host defense system, but also by antibiotic therapy); and variable immunodominant antigenic epitopes of the major outer membrane protein (MOMP) consequently, specific immunity against strains is not produced (therefore multiple reinfection by different serotypes and by the same serotype is possible), but an autopathological immune response may occur [32-35].

As well as hypersensitivity mediated by the T-helper type 2 (Th2) response, which is ineffective and long-lasting, but can lead to tissue damage; the accumulation of heat shock proteins (hsp60) as a consequence of multiple reinfections by *C. trachomatis*, a protein with a high proportion of identity with the human protein, therefore autoimmunity can occur when human tolerance to its own hsp60 is broken; and that the antibodies generated by *C. trachomatis* infection do not inactivate the parasites inside the cells. From the above, it follows that serious sequelae due to chlamydial infection are observed only if it is chronic and persistent inflammation (sustained and harmful possibly due to residual antigens and not the persistence of viable bacteria) is the cause of fibrosis and the scars that characterize all chlamydial diseases [36-39].

One aspect to consider is the proven possibility of co-infection of *C. trachomatis* with other bacteria, especially with *Mycoplasma genitalium* (with high co-infection rates of up to 36%), causing emerging sexually transmitted infection and with high resistance to drugs. In this sense, *M. genitalium*

causes endometrial infection associated with endometriosis due to *C. trachomatis* [40].

Finally, the molecular mechanism of bacterial persistence is pointed out: the deprivation of tryptophan and cysteine, essential amino acids for the expression of late expression proteins such as MOMP and proteins rich in cysteines that cause the cessation of the division of the reticular bodies as well as dedifferentiation of them in elementary bodies, in other words the persistence of *C. trachomatis* is a consequence of undifferentiated intracellular particles; and the abrogation of cell division although DNA replication and segregation persist [32,41].

### Host Immune Response Against *C. trachomatis* Infection

The cellular response is necessary in the resolution of the primary infection, centered on CD4+Th1 lymphocytes, since it produces antichlamydial immunity by allowing greater activation of cytotoxic T lymphocytes and secretion of gamma interferon (INF $\gamma$ ). The participation of CD4+Th2 lymphocytes seems not to be sufficient, since it reduces the infection without resolving it, so it is considered an ineffective response because it does not eliminate reticular bodies or persistent intracellular particles. Without a doubt, the polarization of the immune response towards the Th1 profile requires the secretion of INF $\gamma$  (by natural killer cells) and interleukin-12 (by dendritic cells). It is also known that factors such as cicatricial trachoma in ethnic groups with the allele (IL-10-1082G) favor the Th2 response, favoring the production of IL-10 [42-46].

Humoral immunity also participates in the defense against *C. trachomatis* infection through humoral antibodies, isotypes IgM, IgA, and IgG, of which the first to respond is the secretory IgA at the site of infection, then the IgM participate, IgA and IgG, between 5 and 20 weeks after the infection occurred. In the chronic disease, IgA and IgG are present, in the acute phase the titers are not at constant levels. In the cured infection, only IgG is detected [10, 47].

### Diagnosis

Among the diagnostic tests, the direct staining of the cells obtained from the lesion and the cell culture as a confirmatory diagnostic method (McCoy cell culture) stand out, because in primary genital infections, even of an asymptomatic or subclinical nature, the pathogen can be easily isolated, direct immunofluorescence is also mentioned as a test in this group, due to its speed of application, low cost, high sensitivity (70-100%) and specificity (95%). Recently (the 80's), nucleic acid amplification tests have emerged, specifically the polymerase chain reaction and the ligase chain reaction, with sensitivity and specificity of 100% [48]. The determination of IgA, IgM, and IgG titers is the indirect technique (serology) in the case

of suspected first infection and in epidemiological studies to determine incidence and prevalence of infection in populations [49,50].

It is important to note that amplification technologies without culture and DNA extraction focus on the direct visualization of the microbe by staining with specific antibodies labeled with fluorescein, on the immunohistochemical detection of antigens and detection of hybridization with a DNA probe, among others., and these techniques have the advantages: not requiring extensive experience or facilities to perform cultures, short time to obtain results, and fewer requirements for transporting samples and standardization of the procedure, accompanied by high performance (sensitivity and specificity), but in a lower proportion than bacterial cultures and molecular biology tests [51].

It is recommended to carry out a diagnosis in people at risk of suffering from *C. trachomatis* infection, in those who suffer from other sexually transmitted infections that include their partner, when they have a new sexual partner (last 6 months), when they have more than 2 new partners in the last year, in some clinical conditions (cervicitis, urethritis, and infertility), in cytology with atypical cells suspicious of human papillomavirus or cervical cancer, and during pregnancy [52-54].

## Treatment

The treatment is based on antibiotics capable of penetrating the lipophilic plasma membranes in order to reach the reticular bodies (reproductive phase), which are metabolically active and therefore susceptible to the action of these medications. In this sense, are used, cyclines (doxycycline and tetracycline), quinolones (ciprofloxacin, ofloxacin and levofloxacin) and macrolides (erythromycin and azithromycin). Amoxicillin is only used in pregnant women [54].

With the administration of antibiotics, microbiological cure rates are obtained that exceed 70% depending on the drug administered, however, therapeutic failures may occur that result in chronicity of the disease and the persistence of the bacteria for many years, associated with these failures: the age of the patient, nutrient restriction (iron) and the renewal of sexual activity as indirect factors, and heterotypic bacterial resistance as direct factors (only 1% of the bacterial population is multiresistant, less metabolically active forms of *C. trachomatis*), recurrences with the same genotype (D, I, Ia, H, and Ja, these serotypes can persist for several years regardless of the treatment), low adhesion, pharmacokinetics and tissue availability of the drug, this last factor has been combated with the encapsulation of the antibiotic in liposomes (they allow direct transport to the site of infection and avoid the loss of the antibiotic due to interaction with proteins) [55-61].

It has also been pointed out that penicillin, ofloxacin, and

ciprofloxacin participate in the induction of persistence of bacterial infection by *C. trachomatis*, since they generate the so-called forms of penicillin (enlarged and aberrant reticulated bodies, possibly due to the inhibition of the synthesis of peptidoglycan), which after the suspension of these antibiotics resume normal growth, then it can be noted that some antibiotics used in the treatment of *C. trachomatis* infection favor its persistence instead of resolving the infection [62-66].

## Conclusions

*C. trachomatis* infection continues to be the most frequently observed in sexual transmission with high prevalence rates in low-income countries, more frequent in women and in the age group between 15 and 19 years, except for in those countries that have adopted health control programs, the trend is towards an increase in the number of cases. *C. trachomatis* is considered an obligate intracellular gram-negative bacterium, although it is phylogenetically distinct. The clinical, diagnostic, and epidemiological importance of the identification and classification of different *C. trachomatis* isolates is recognized in establishing test parameters for cure, persistent infections versus reinfection and its role in complications. Rapid non-invasive diagnostic tests are required to detect infection in asymptomatic individuals. There are several strategies that *C. trachomatis* uses to ensure its persistence in the host and produce chronic infection and clinical complications.

The resolution of the primary infection, that centered on CD4+Th1 lymphocytes, corresponds to the cellular response. In terms of diagnosis, the isolation or direct visualization of the bacteria is the recommended test, however, molecular biology methods based on the amplification of nucleic acids with significantly high sensitivity and specificity are currently emerging, and serological tests continue to be used in studies risk populations. In relation to treatment, the recommended antibiotics are those capable of penetrating the lipophilic plasma membranes and the bacterial forms sensitive to these, the reticular bodies. The percentage of cure with specific antibiotic therapy can exceed 70%, however, therapeutic failures are reported that culminate in chronicity of the disease and complications. There are many aspects to be revealed in terms of pathogenesis, biology of the microbial agent, and treatment, hence the need to generate new knowledge in this regard and to present thematic consolidations as was done in this article.

## Conflict of Interest

The authors declare that there are no conflicts of interest.

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