

Chlamydial infections and prostatitis in men

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INTRODUCTION AND TAXONOMY

Chlamydiae are obligate intracellularly growing bacteria; currently four species are recognized: *C. pneumoniae*, *C. trachomatis*, *C. psittaci* and *C. pecorum*, of the genus *Chlamydia* of the family Chlamydiaceae within the order Chlamydiales [1]. *C. trachomatis* is a major cause of trachoma and sexually transmitted diseases (STDs) in humans [1]. Two biovariants of *C. trachomatis* exist within the human-specific strains, which together consist of 15 serovariants. Among the trachoma biovar, serovars A, B, Ba and C are associated with ocular infection, and serovars D–K are associated with urogenital infection. Serovars L1, L2 and L3 comprise the lymphogranuloma venereum biovar [2].

EPIDEMIOLOGY

Genital *C. trachomatis* infections are among the most common STDs worldwide; it is currently estimated that ≈4 million new chlamydial infections occur each year in the USA, at an estimated annual cost of >2.4 billion dollars [3]. Table 1 [4] shows the diseases caused by *C. trachomatis* serovars D–K in women, men and newborns. The prevalence in symptomatic women is 13–18% and in asymptomatic women ≈5% [5]. Similarly, the prevalence in asymptomatic men is 5–7% [6].

PATHOPHYSIOLOGY

The chlamydiae undergo a unique developmental cycle. After uptake, chlamydiae develop in a so-called elementary body (EB) and grow within an intracellular vacuole, termed an inclusion [7]. The EB is infectious but is metabolically inactive and cannot replicate. This form differentiates

upon infection into the non-infectious but metabolically active replicating reticulate body (RB) [7]. Within the first 2–6 h after internalization, EBs begin differentiating into RBs. Over the next several hours, RBs increase in number and size, until after 18–24 h the numbers of RBs are maximal [7]. After 24–48 h more RBs begin differentiating back to EBs [7]. The infected cell ruptures at 48–72 h after infection, and the infectious EBs are released again. An intense and chronic inflammation is elicited and maintained [8].

DIAGNOSIS

Laboratory testing of *C. trachomatis* has traditionally consisted of cell culture of inocula prepared from urogenital specimens, and later antigen and nucleic acid detection technologies were developed. The nucleic acid amplification technologies have promoted the widespread use of detection methods for *C. trachomatis*. Molecular investigation techniques for *C. trachomatis* have currently been accepted as the standard. The detection of *C. trachomatis* in prostatic secretions for the diagnosis of prostatitis has always been limited because potential contamination occurs by the passage of the specimens through the urethra [9].

CULTURE

Culture detects only viable infectious chlamydial EBs. The sensitivity is at most 70–85% and the specificity approaches 100%. The low sensitivity, costs, the high level of technical expertise necessary and time required to obtain results, are significant disadvantages of this method. The advantage of culture is that additional investigations, such as genotyping or susceptibility testing, can be done [3].

NO-CULTURE, NON-NUCLEIC ACID AMPLIFICATION TECHNOLOGIES

These technologies are based on direct visualization of the chlamydial organism by staining with fluorescein-labelled specific antibodies.

In the *direct cytological examination* (direct fluorescent antibody, DFA) technique monoclonal antibodies are directed either to the major outer membrane protein (MOMP) or the lipopolysaccharide (LPS) antigens of *Chlamydia*. The sensitivity of the DFA against the MOMP of *C. trachomatis* is 80–90% and the specificity is 98–99% relative to culture. The DFA test is rapid, and can be done within 30 min, but the microscopic evaluation is laborious and requires experienced personnel [3].

The *immunohistochemical detection of antigen* (enzyme immunoassay, EIA) diagnostic test is based on the immunochemical detection of LPS genus-specific antigen. The sensitivity of the EIA of male urethral *C. trachomatis* infection is 43–92% and the specificity ≈97% relative to culture [3].

Rapid (near-to-patient) tests are used in the physician's office and are based primarily on membrane capture or latex immunodiffusion. Various tests are available and are generally not well evaluated. Studies showed that these tests are significantly less sensitive and specific than laboratory-based EIAs [3].

NUCLEIC ACID DETECTION METHODS

In the commercially available *DNA hybridization* method for detecting *C. trachomatis* (PACE 2, General-Probe, San Diego, CA, USA) a chemiluminescent DNA probe is used. The sensitivity of this method for male urethral *C. trachomatis* infection is 85% and the specificity ≈99% relative to culture. The sensitivity relative to a DNA amplification standard is reportedly 77–93% [3].

The most widely known of the *DNA amplification* technologies is PCR; the PCR test uses two synthetic oligonucleotide primers with sequences that are complementary to flanking regions of a specific DNA segment present in the target organism. There are several target antigens for the PCR technology in *C. trachomatis*.

In the Amplicor test (Roche Diagnostics), primers target a segment of the cryptic plasmid DNA present in *C. trachomatis* strains. The Amplicor PCR has been evaluated for both urogenital and urine specimens; the sensitivity is 90% and the specificity 99–100% relative to an expanded culture standard. Another target is the MOMP gene; the MOMP PCR is somewhat less sensitive, but the MOMP gene can be amplified almost in full length and this method can therefore be used for epidemiological investigations [3].

The polymerase can be inhibited by different substances in the specimen in ≈5% of samples [10] and therefore the ligase chain reaction (LCR, Abbot Laboratories, USA) was developed which also targets the *C. trachomatis* plasmid. In the LCR test, four synthetic oligonucleotide probes (two per DNA strand) anneal at the plasmid DNA. There is inhibition of the probes in ≈2.5% of samples. The sensitivity of urine specimens is 94%, and the specificity 99–100% relative to an expanded standard method [3]. However, in general, study data suggest that both PCR and LCR technologies will perform similarly for both urogenital and urine specimens. All nucleic acid amplification technologies detect nucleic acid targets and do not depend on the viability of the organism.

SEROLOGICAL TESTS

Systemic serological tests are generally not useful in the diagnosis of genital tract infections caused by *C. trachomatis*, because antibodies elicited by *C. trachomatis* are long-lived and a positive antibody test will not distinguish a previous from a current infection [3].

The *complement fixation* test detects complement-fixing antibodies that recognize the genus-specific LPS antigen and is not specific for any one chlamydial species [3].

The *microimmunofluorescence* (MIF) test detects species- and serovar-specific antibodies that probably react with species- and serovar-specific epitopes in chlamydial MOMP. The test is highly reliable in all populations for detecting a previous exposure to chlamydiae by the presence of IgG antibodies. IgM antibodies are usually not present in patients with genital tract infections unless they represent the first exposure of the individual [3].

Women	Men	Newborn	TABLE 1 Diseases caused by <i>C. trachomatis</i> serovars D–K in women, men and newborns. From [4]
urethritis	urethritis	preterm delivery	
cervicitis	epididymitis	conjunctivitis	PID, pelvic inflammatory disease.
adnexitis/PID	prostatitis	pneumonia	
ectopic pregnancy			
infertility	infertility		
perihepatitis			
reactive arthritis	reactive arthritis		
Reiter's syndrome	Reiter's syndrome		

The *EIA test* detects reactivity to genus-specific antigen, or LPS, of chlamydial elementary or reticulate bodies. The test is not specific for *C. trachomatis* [3].

Modern *C. trachomatis* peptide-ELISAs using a synthetic peptide from the immunodominant region of the MOMP seems to be able to discriminate *C. trachomatis*-specific antibodies in urethral secretions [11].

The Centers for Disease Control have provided recommendations for additional testing and patient management after a positive screening test [12]

- All positive screening tests should be considered presumptive evidence of infection.
- An additional test should be considered after a positive screening test if a false-positive screening test would result in substantial adverse medical, social or psychological impact for a patient.
- Consideration should be given to routine use of an additional test after a positive screening test if the positive predictive value is considered low (e.g. <90%).
- Patients should be counselled about prompt treatment after a positive screening test because an additional test might be falsely negative.

UROGENITAL DISEASES IN MEN

URETHRITIS

Urethritis is the result of initial infection with *C. trachomatis* in the male and can ascend from there to the contiguous urogenital organs. The clinical presentation includes dysuria, frequency and urethral pain with no voiding. Urethral discharge may or may not be present; 50–70% of infections due to *C. trachomatis* in males produce no symptoms [13]. The male urethra contains all the necessary components for antigen

presentation and humoral and cellular immune response. However, urethral infection with *C. trachomatis* induces a weak immunological response in humans.

PROSTATITIS

The prostatitis syndrome is one of the most common entities encountered in urological practice. Classification of the prostatitis syndrome is based on the clinical presentation of the patient, the presence or absence of white blood cells in the expressed prostatic secretion, and the presence or absence of bacteria in the secretion [14]. Depending upon the duration of symptoms, prostatitis is described as either acute or, where symptoms are present for ≥3 months, chronic. Referring to the classification of the prostatitis syndrome suggested by the National Institute of Diabetes and Digestive and Kidney Diseases/National Institutes of Health, bacterial prostatitis (acute and chronic) is distinguished from chronic pelvic pain syndrome [15]. It is still debated if and to what extent *C. trachomatis* can cause prostatitis. The definitive association between the isolation of *C. trachomatis* and a prostatic origin is limited because diagnostic material from the prostate may reflect only urethral contamination [16].

C. trachomatis in specimens obtained via the urethra

Material obtained after passage down the urethra has been studied [9]; in up to 27% of the cases, chlamydial isolation has been associated with infections to the prostate [17]. Therefore, *C. trachomatis* may originate in the prostate in an unknown proportion of patients with prostatitis symptoms. Because the urethral infection is the origin for ascending infection to the prostate, a discrimination between urethral and prostatic infection is impossible with this approach.

C. trachomatis in prostatic biopsies

Therefore, in another approach prostatic tissue was obtained from patients with different types of prostatitis; *C. trachomatis* was detected in 3–30% of the patients [9]. The discrepant results might be due to the different techniques used to retrieve the prostatic tissue. Whereas tissue from transrectal biopsies, TURP or open surgery might contain epithelial cells from the prostatic urethra, which could have been infected in the course of urethral infection, only in perineal biopsies from the peripheral lobes of the prostate can urethral contamination be excluded.

C. trachomatis in semen

It is generally accepted that chlamydia may ascend to the epididymis, may adhere to human spermatozoa and may enter spermatozoa [18]. However, in any case the ejaculate has to pass through the urethra, becoming potentially contaminated on its way.

Immune responses to *C. trachomatis*

Only the MIF test is thought to be able to detect local antibodies on an original type-specified basis. Using the MIF test 7% of andrological patients had seminal antibodies against *C. trachomatis* alone [9]. Using the peptide-ELISA, elevated titres of *C. trachomatis*-specific secretory IgA were identified in acute genital infections [11]. Local secretory IgA-antibodies against *C. trachomatis* have been evaluated in prostatic secretions and seminal plasma in patients with prostatitis, epididymitis, or infertility [9], but only some of the IgA-positive specimens were positive in PCR-investigations.

EPIDIDYMITIS

C. trachomatis is reported in up to 30% of patients with epididymitis [19]. The symptoms involve subacute to chronic scrotal pain and epididymis oedema. Epididymitis caused by *C. trachomatis* can cause significant andrological sequelae.

INFERTILITY

The *in vitro* exposure of spermatozoa to EBs of *C. trachomatis* can lead to sperm death. *In vivo* analyses showed that *C. trachomatis* is associated with sperm pathology [20].

C. trachomatis IgG antibodies in the man of infertile couples was related to decreased pregnancy rates and to the presence of IgG antibodies in the woman [21].

REACTIVE ARTHRITIS AND REITER'S SYNDROME

Especially in the male, infection with *C. trachomatis* can lead to reactive arthritis or Reiter's syndrome. Predominantly peripheral joints are affected unilaterally in >60% of infections. *C. trachomatis* was found in up to 25% of patients with ankylosing spondylitis [22].

THERAPY

European guidelines for managing chlamydial infection have been issued [23]; the following indications for treatment have been devised: Confirmed oculogenital *C. trachomatis* infection; infection with *C. trachomatis* in the partner; if laboratory tests for *C. trachomatis* are not available in a patient with a confirmed *Neisseria gonorrhoeae* infection; if laboratory tests for *C. trachomatis* are not available in a patient with clinical signs of a chlamydial infection.

Chlamydia are only metabolically active in the host cell and therefore only targeted intracellularly by antibiotics. Intracellularly accumulated antibiotics are tetracyclines, macrolides and quinolones.

First-line regimens include:

- Azithromycin 1 g orally, single dose, or
- Doxycycline 100 mg orally twice a day for 7 days

Alternative regimens are:

- Erythromycin base 500 mg orally four times a day for 7 days, or
- Ofloxacin 200 mg orally twice a day for 7 days, or
- Roxithromycin 150 mg orally twice a day for 7 days, or
- Clarithromycin 250 mg orally twice a day for 7 days

Although ofloxacin is generally recommended, levofloxacin has excellent activity against *C. trachomatis*.

Abstinence from sexual intercourse should last for 7 days and until all current partners have received satisfactory treatment [23].

PREVENTION

Asymptomatic infections are common and can only be detected by screening. If symptomatic infection is present, the following points should be considered: (i) Laboratory diagnosis to increase the reliability of the clinical diagnosis, which may have serious implications for the patient and their sexual partners. (ii) Therapy should be started appropriately as recommended and at the initial consultation, if a diagnosis can be made at that visit, and if epidemiological treatment is indicated as a result of a diagnosis in a sexual partner. (iii) Partner notification should be considered in confirmed cases. (iv) The follow-up should be done to confirm the efficacy of therapy and to decide whether follow-up testing might be indicated. (v) Epidemiology should be assessed to allow greater accuracy in the notification of infections, and in the return of epidemiological data to public-health agencies [24].

CONCLUSION

C. trachomatis is the most frequent cause for STDs in European countries. Diseases caused by *C. trachomatis* range from asymptomatic to those with severe sequelae. Especially in prostatitis the exact role is still under debate because of the technical difficulties in localizing the pathogen to the prostate. For treatment only some antibiotics are effective because of the intracellular habitat of the pathogen. Preventing infection is a serious issue and comprises treatment and screening efforts.

CONFLICT OF INTEREST

None declared.

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Abbreviations: STD, sexually transmitted disease; EB, elementary body; RB, reticulate body; DFA, direct fluorescent antibody; MOMP, major outer membrane protein; LPS, lipopolysaccharide; EIA, enzyme immunoassay; LCR, ligase chain reaction; MIF, microimmunofluorescence.