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JSM Microbiology

Review Article

The Role of Chlamydia Trachomatis Infection in Young Men: What we Need to Know?

Tommaso Cai[1]*, Sandra Mazzoli[2], Irene Tamanini[1], Paolo Verze[3], Vincenzo Mirone[3], Cesare Selli[4] and Riccardo Bartoletti[5]

[1]*Department of Urology, Santa Chiara Regional Hospital, Italy*
[2]*Sexually Transmitted Diseases (STD) Centre, Santa Maria Annunziata Hospital, Italy*
[3]*Department of Urology, University of Federico II, Italy*
[4]*Department of Urology, University of Pisa, Italy*
[5]*Department of Urology, University of Florence, Italy*

***Corresponding author**
Tommaso Cai, Department of Urology, Santa Chiara Hospital, Trento, Italy, Largo Medaglie d'Oro 9, Tel:+39 0461 903306; Fax: +39 0461 903101; Email: ktommy@libero.it

Submitted: 05 December 2014

Accepted: 13 January 2015

Published: 15 January 2015

Keywords

- *Chlamydia thracomatis*
- Prostate
- Male
- Fertility
- Treatment
- Review

Abstract

Chlamydia trachomatis infections are the most common sexually transmitted bacterial infections worldwide. Because *Chlamydia trachomatis* infections are asymptomatic in approximately 50% of infected men and 70% of infected women, there is a high risk for reproductive tract sequelae and high diffusion of the disease. Recently, some studies improved the comprehension of this infection and its natural history highlighting the fact that severe complications can be avoided only by a proper early diagnosis and appropriate treatment. We reviewed the literature relating to the new findings in the treatment of *Chlamydia trachomatis* infection in sexually active young men. Articles from 1960–2014 were identified through a Medline search using the keyword "*Chlamydia trachomatis*" combined with "urethritis", "epididymitis", "prostatitis", "treatment", or "management". Several studies highlighted that Chlamydia are only metabolically active in the host cell and therefore only targeted intracellularly by antibiotics. However, even if the standard therapy includes intracellulary-accumulated antibiotics such as tetracyclines or macrolides, recent evidences highlight the role of quinolones. In particular, recent studies highlight the role of prulifloxacin in the treatment of chronic prostatitis patients for improving patient's quality of life and decreasing the IL-8 level. However, there is a need for future studies and to diffuse the knowledge about *Chlamydia trachomatis* especially in urological clinical practice, in order to reduce the risk for failure diagnosis.

INTRODUCTION

Chlamydia trachomatis (Ct) is the most common sexually transmitted bacterium worldwide with over three million new infections per year [1-2]. In particular, Chlamydia is the most frequently reported sexually transmitted infection in Europe and the number of cases is steadily increasing, with more than 255,000 cases in people below 25 years of age [3]. The rate of transmission between sexual partners may be as high as 75% [4]. However, approximately 75% of Ct infections in women and up to 50% of those in men are asymptomatic [5,6]. This aspect is extremely important due to the fact that although up to 13.3% of young men may have a genital chlamydial infection, only half of these will present with any symptoms—and even fewer are likely to pursue treatment [7]. Moreover, absence of symptoms increases the risk of infecting sexual partners and may cause long-term complications in men too, such as poor quality of semen and infertility [8-10]. Furthermore, several factors contribute to make difficult detecting Ct by a conventional analysis [11]. To date, the DNA recombination techniques are universally accepted as the gold standard to evaluate the presence of Ct in biologic samples [12], even if immunologic markers of Ct infection such as immunoglobulin A (IgA) antibody and cytokines have been detected in total ejaculate and seminal plasma samples to demonstrate their role in monitoring men with chronic prostatitis (CP) [13,14]. The European Urological Association and the Centres for Disease Control and Prevention guidelines recommendedthe use of doxycycline and azithromycin in the treatment of chlamydial infections [3,15].

However, in management and treatment of patients affected by Ct infections the following factors should be taken into account:

1) Chlamydia are only metabolically active in the host cell and therefore only targeted intracellularly by antibiotics

2) Intracellular-accumulated antibiotics are tetracyclines,

macrolides and quinolones [3,15].

Even if doxycycline and azithromycin are the most widely prescribed drugs in Ct infections treatment and recommended as the primary approach, other fluoroquinolones such as ofloxacin, levofloxacin or prulifloxacin are suggested as alternative drugs [3,16].

We need, also, to take into account that the management of Ct infection should include:

1. treatment of patients (to reduce complications and prevent transmission to sex partners)
2. treatment of sex partners (to prevent reinfection of the index patient and infection of other partners)
3. risk-reduction counselling
4. Repeat chlamydial testing in women a few months after treatment (to identify recurrent/persistent infections) [17-18].

For these reasons, Ct represents a challengingmanagement for the physicians. Here, we aimed to summarize the most current developments in the therapeutic approaches in Ct infections in sexually active young men.

MATERIALS AND METHODS

Evidence acquisition

We conducted a search of the English-language literature from 1960 through December 2014 with use of the Medline computerized database of the US National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed). The Medline search has been carried-out by using the following Medical Subject Headings and free text terms: *Chlamydia trachomatis*, and chlamydia infections (exploded) were combined with the terms treatment, therapy, antibiotic, drug, quinolones,

Tetracycline and then limited to humans, male and young adult: 19-24 years. Moreover, we searched reference lists of articles to identify potential additional references. All original paper and review studies of Ct treatment in young adult have been considered for this review. We considered also guidelines from the National Institute for Health and Clinical Excellence, the European Centre for Disease Prevention and Control, the US Centres for Disease Control and Prevention, World Health Organization and European Association of Urology. From an initial literature search with114 unique citations, a total of 27 articles were selected for the present review.

RESULTS

Recommendations for the clinical practice

Symptoms: Even if more than 50% of men are asymptomatic, the most common clinical features of *Chlamydia trachomatis* infection in men are:

1. burning with micturition
2. 'penile tip irritation'
3. watery, viscous excretion ('morning milker')
4. Urethral discharge and proctitis [19,20].

Diagnosis: The method of choice for *Chlamydia trachomatis* detection is nucleic acid amplification testing (NAATs). However, NAATs tests generally show two important drawbacks: the cost and the presence of inhibitors in specimens. However, they show a high specificity [21]. Finally, in 2006, a new C. trachomatis variant belonging to serovar E, with a 377-bp deletion in the cryptic plasmid, was described in Sweden [22]. This new variant can obviously not be detected by amplification tests targeting the deleted area, but can be detected by amplification targeting a chromosomal gene, e.g. ompA or arRNA gene [22]. However, new versions of the COBAS Taqman v2.0 test and of the Abbott test allow simultaneous detection of the cryptic plasmid and of ompA, and simultaneous detection of two different regions of the cryptic plasmid, respectively [22].

What is the best kind of biological sample to collect and analyse?

First-void urine is the preferred specimen for the diagnosis of urogenital Chlamydia trachomatis infection in men and female [15]. However, in men some authors suggest to use the biological samples obtained from Meares-Stamey test, as described by Mazzoli [23]. The accuracy of urethral swab is, today, clinically irrelevant [15].

Therapy

Even if several Authors stated that many infections could spontaneously clear over time [24], the natural course of infection has not been studied in great detail and some infections may proceed to a chronic persistent state [25]. Recently, the European guidelines for managing chlamydial infection have been issued [26]; the following indications for treatment have been devised:

- confirmed genital Ct infection

- Infection with Ct in the partner

- If laboratory tests for Ct are not available in a patient with a confirmed *Neisseria gonorrhoeae* infection

- If laboratory tests for Ct are not available in a patient with clinical signs of a chlamydial infection.

First-line regimens include: Azithromycin 1 g orally, single dose or Doxycycline 100 mg orally twice a day for 7 days. Several alternative regimens have been purposed: 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 or Levofloxacin 500 mg once daily for 7 days or Ofloxacin 300 mg twice a day for 7 days [26-28]. Men and women with a diagnosis of Ct infection should be offered a complete work-up for other STIs, such as gonorrhoea, syphilis, mycoplasmata and HIV [26]. In case of co-infection with *Mycoplasma genitalium* is confirmed, patients should not betreated with a single dose of 1 g azithromycin, but with ashort course of azithromycin: 500 mg on day 1 followed by250 mg on days 2–5 (level III, grade C) [26,29]. In case of treatment failure, a repeated course or a longer course (10–14 days) with doxycycline or a macrolide has been suggested, but evidence is lacking (level IV) [26]. The most common reason for therapy failure is re-infection from an untreated partner (level II) [26,30]. An interesting suggestion is the combineduse of rifampicin and a macrolide [31].

Aspects under discussion

Even if there is a consensus about the first-line treatment regiments, future studies are need in case of treatment failure or infection persistence.

What about treatment?

Although little is known about Ct survival in the presence of fluoroquinolones, it is well known that after multiple cultivation passages resistant mutant for some fluoroquinolones were determined [32]. In a recent report, Smelov and co-workers suggested that ofloxacin could be recommended as the primary drug in the treatment of chlamydia-infected patients with CP, due to its pharmacokinetic parameters [32]. Moreover, the same Authors stated that the decision on the prescription of pefloxacin or lomefloxacin should be made individually, but ciprofloxacin treatment is not suggested [32]. The authors, however, concluded that the conditions of in vitro susceptibility studies are incompatible with the infection as it occurs *in vivo* even if could be useful to include investigations for antibiotic susceptibility in every patient prior to treatment [32]. Recently Cai *et al*., by means of a prospective, randomized and open-label study on 221 patients affected by chronic prostatitis due to Ct infection who had undergone oral administered prulifloxacin 600 mg once daily for 14 days or doxycycline 100 mg orally twice daily for 21 days, found that prulifloxacin was equivalent to the standard therapy [16]. In this study, moreover, the authors showed that prulifloxacin was superior over standard therapy in microbiological efficacy rates in terms of mucosal IgA and IL-8 levels decreasing [16]. This effect should be probably, due to an anti-inflammatory effect of quinolones.

What about IL-8?

The role of pro-inflammatory cytokines such as IL-6 or IL-8 in Ct infection is well established, discussed and used not only in the diagnosis phase but also in management and therapy control [11,16,33]. Several reports, moreover, suggestedthat IL-8 evaluation should be used, notonly as a Ct infection marker, but also as a marker of therapy efficacy [11,16]. The role ofmolecular markers in the management of Ctinfections is, thus, clinically useful and suggested. Mazzoli et al., recently, demonstrated that patients who had reported the higher mean value for IL-8 and massive presence of mucosal IgA, making evident a strong inflammation and a correlation with the higher level of pain and a worse quality of life, with a significant correlation between IL-8 and IgA values and NIH-CPSI subscale scores [11]. Moreover, in the clinical practice, Cai *et al*. found a good relationship between IL-8 and NIH-CPSI, demonstrating that an improvement in QoL (NIH-CPSI decreasing) is related to a decrease in IL-8 levels after therapy [16]. Even if some authors stated that IL-8 evaluation could be a good prognostic marker of response to therapy, the use of IL-8 is not entered into everyday clinical practice. Future studies are needed in order to diffuse the use of this method.

What about mucosal IgA?

Some authors demonstrated, in an animal model, that high production of IgA in genital tract secretions seems related to the presence, persistence, and accumulation of Th2 MoPn cells in the genital tract during chronic infections, with the consequent inability to clear the infection [33]. Particularly, the presence of chronic infection in patients affected by Ct infection has been wellcorrelated with the presence of high levels of anti-Heat Shock Protein 60 (anti-HSP60) and MOMP2 mucosal IgA antibodies. The anti-HSP60 immunization suggests chronic or repeated stimulation from an endemic source of the microorganism, proved by the presence of Ct DNA found in young sexually active patients affected by chronic prostatitis due to Ct infection [34]. The use of anti-Ct mucosal IgA evaluation is available in some laboratories for the everyday clinical practice.

What about complication treatment?

It is well known that chronic prostatitis due to Ct infection not only decreases the quality of life [35] but also has a significant impact on a couple's reproductive health [8]. Indeed, Ct has a significant role in male infertility, and eradication of the infection is critical to the recovery of the man's fertility [36]. However, eradication of the infection after antibiotic therapy does not always result in recovery ofsemen quality, and other compounds are consequently needed. Recently, Cai *et al*., by using a prospective, randomized, and controlled study, demonstrated that L-arginine, L-carnitine, acetyl-L-carnitine, and ginseng extracts together with prulifloxacin improved semen parameters in patients with Ct genital infection and oligoasthenoteratozoospermia compared to treatment with prulifloxacin therapy alone [37]. The enhanced quality of spermatozoa from an infertile status to a normal fertility index could be determined through two mechanisms. The anti-inflammatory and antioxidative effects of ginseng could improve the shape and concentration of spermatozoa [38], and L-arginine, L-carnitine, and acetyl-L-carnitine could enhance sperm motility and function by stimulating the activity of endothelial nitric oxide (NO) synthase [39]. Two important aspects in the treatment of male infertility inpatients affected by chronic prostatits and oligoasthenoteratozoospermia due to Ct infection should be discussed. Firstly, treatment should be started concurrently with the antibiotic treatment. Secondly, the association of antibiotic therapy with L-arginine, L-carnitine, acetyl-L-carnitine, and ginseng extracts together can produce good results in terms of semen quality recovery [37]. Recently, Miyashita et al. demonstrated the efficacy of a new-generation fluoroquinolone, named sitafloxacin against Ct infection [40]. Its antimicrobial activity is unique compared to those of conventional fluoroquinolones, even if few clinical studies have been reported [41,42]. In a recent study, the microbiological eradications rates of Ct, M. genitalium and U. urealyticum were 100 % (33 of 33), 100 % (11 of 11) and 80 % (8 of 10), respectively [43]. Even if these results are promising, few clinical studies have been reported in the treatment of patients affected by non-gonococcal urethritis and no study in those with chronic prostatitis due to Ct infection.

Where we have to go?

The asymptomatic nature of Ct makes diagnosis and prevention of sequelae a challenge for the urologist. It is well known that host immunity induced by chlamydial infections is not long lasting and may take several months or years to develop [44,45]. Moreover, the pathogenesis of Ct has not been completely elucidated, and the role of host immunology is unclear [45]. Several chlamydial vaccine trials have usedthe major outer membrane protein as a vaccine candidate [45]. However, studies

using the major outer membrane protein have been inconclusive and immunity is generally short-lived [45].

SHORT MESSAGES TO TAKE HOME

- *Chlamydia trachomatis* infection is most prevalent sexually transmitted bacterial infections worldwide.
- *Chlamydia trachomatis* infection has a significant impact on young male fertility.
- First-line treatment includes: Azithromycin 1 g orally, single dose, or Doxycycline 100 mg orally twice a day for 7 days.
- A treatment schedule with prulifloxacin 600 mg once daily for 14 day is equivalent to the standard therapy.
- IL-8 evaluation should be used as a marker of therapy efficacy.
- Phytotherapeutic agents should be able to improve semen parameters in patients with *Chlamydia trachomatis* genital infection and oligoasthenoteratozoospermia when administered together with antibiotic treatment.

ACKNOWLEDGEMENTS

We are grateful to all Santa Chiara Hospital, Department of Urology members for their assistance and to Professor John Denton for manuscript language revision.

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Cite this article

Cai T, Mazzoli S, Tamanini I, Verze P, Mirone V, et al. (2015) The Role of Chlamydia Trachomatis Infection in Young Men: What we Need to Know? JSM Microbiology 3(1): 1017.