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Chlamydial infections in urological disease: A challenging management

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Abstract

Chlamydia trachomatis (Ct) infections are the most prevalent sexually transmitted bacterial infections worldwide, causing considerable morbidity and socioeconomic problems. Moreover, Ct infections are asymptomatic in approximately 50% of infected men and 70% of infected women, with the risk for reproductive tract sequelae both in women and men. Recent studies have improved the comprehension of this infection and its natural history, also highlighting its role in decreasing male fertility. 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 Ct infection in sexually active young men. Articles from 1960-2012 were identified through a Medline search using the keywords "*Chlamydia trachomatis*" combined with "urethritis", "epididymitis", "prostatitis", "treatment" or "management". Currently, several studies have been published about the role of new antibiotic schedules and new associated compounds in order to improve the efficacy in terms of microbiological results and patient quality of life. In particular, several studies stress the fact that Chlamydia is only metabolically active in the host cell and therefore only targeted intracellularly by antibiotics. Even although the standard therapy includes intracellularly-accumulated antibiotics such as tetracyclines or macrolides, recent evidence highlights the role of quinolones. In particular, recent studies highlight the role of prulifloxacin in the treatment of chronic prostatitis for improving the patient's quality of life and decreasing the IL-8 level. However, future studies should focus on delineating the natural history of recurrent infections, paying particular attention to treatment failures.

Key words: Chlamydia trachomatis; Prostate; Male; Fertility; Treatment; Review

Core tip: *Chlamydia trachomatis* (Ct) infection is the most prevalent sexually transmitted bacterial infection worldwide with a significant impact on young male fertility. Ct represents a challenge for the urologist, both for diagnosis and treatment. An accurate comprehension of the pathology, diagnosis and treatment of this entity is essential for the urologist in order to prevent persistent consequences and improve the patient's quality of life. We summarize the most current developments in the treatment of young men affected by chronic prostatitis due to Ct infection.

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INTRODUCTION

Chlamydia trachomatis (Ct) is the most common sexually transmitted bacterium worldwide, with over three million new infections per year[1,2]. The World Health Organization estimates that 92 million new cases of Chlamydia occur worldwide every year[3]. In particular, Chlamydia is the most frequently reported sexually transmitted infection in Europe and the number of cases is steadily increasing, with more than 255000 cases in people below 25 years of age[4]. The rate of transmission between sexual partners may be as high as 75%[5]. Therefore, partner notification and subsequent treatment are very important. However, approximately 75% of Ct infections in women and up to 50% of those in men are asymptomatic[6,7]. 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[8]. Moreover, the absence of symptoms increases the risk of infecting sexual partners and may also cause long-term complications in men, such as poor quality of semen and infertility[9-11]. Furthermore, several factors contribute to make it difficult to detect Ct by a conventional analysis[12]. To date, DNA recombination techniques are universally accepted as the gold standard to evaluate the presence of Ct in biological samples[13], even although immunological 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)[14,15]. A recent review suggested that antimicrobial groups effective against Ct include the macrolides, tetracyclines, quinolones and penicillins[16,17]. The European Urological Association and the Centers for Disease Control and Prevention guidelines recommended the use of doxycycline and azithromycin in the treatment of chlamydial infections[4,18]. However, in the management and treatment of patients affected by Ct infections, the following factors should be taken into account: (1) chlamydia is only metabolically active in the host cell and therefore only targeted intracellularly by antibiotics; and (2) intracellularly-accumulated antibiotics are tetracyclines, macrolides and quinolones[4,18]. Although 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[4,19]. However, the approach to 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 counseling; and (4) repeat chlamydial testing in women a few months after treatment (to identify recurrent/persistent infections)[20,21]. For these reasons, management of Ct is challenging for the urologist. We summarize the most current developments in the therapeutic approaches in Ct infections in sexually active young men.

EVIDENCE ACQUISITION

We conducted a search of the English language literature from 1960 through December 2010 with use of the Medline computerized database of the US National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed). The Medline search was carried out using the following medical subject headings and free text terms. Ct and chlamydia infections (exploded) were combined with the terms treatment, therapy, antibiotic, drug, quinolones and tetracycline, 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 papers and review studies of Ct treatment in young adults were considered for this review. We also considered guidelines from the National Institute for Health and Clinical Excellence, the European Center for Disease Prevention and Control, the US Center for Disease Control and Prevention, World Health Organization and European Association of Urology. From an initial literature search with 139 unique citations, a total of 19 articles were selected for the present review. A matched search between Ct and chlamydia infections (exploded) and quinolones found 3 articles.

RECOMMENDATIONS FROM THE INTERNATIONAL GUIDELINES

The Ct infection clinical features in men are: more than 50% are asymptomatic; burning with micturition; "penile tip irritation"; watery, viscous excretion ("morning milker"); urethral discharge; and proctitis[22,23]. Although 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 were issued[26]. The following indications for treatment were devised: (1) confirmed genital Ct infection; (2) infection with Ct in the partner; (3) in a patient with a confirmed *Neisseria gonorrhoeae* infection if laboratory tests for Ct are not available; and (4) in a patient with clinical signs of a chlamydial infection if laboratory tests for Ct are not available.

First line regimens include azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice a day for 7 d. Several alternative regimens have been proposed: erythromycin base 500 mg orally four times a day for 7 d; ofloxacin 200 mg orally twice a day for 7 d; roxithro-

mycin 150 mg orally twice a day for 7 d; clarithromycin 250 mg orally twice a day for 7 d; levofloxacin 500 mg once daily for 7 d; or ofloxacin 300 mg twice a day for 7 d [17,20,26].

Co-infections with other sexually transmitted infections

Men and women with a diagnosis of Ct infection should be offered a complete work-up for other sexually transmitted infections, such as gonorrhea, syphilis, mycoplasmata, human papillomavirus and HIV[11,26]. If co-infection with *Mycoplasma genitalium* is confirmed, patients should not be treated with a single dose of 1 g azithromycin, but with a short course of azithromycin: 500 mg on day 1 followed by 250 mg on days 2-5 (level Ⅲ, grade C) [26,27].

Rectal Ct infection

In cases of rectal non-LGV chlamydial infections, the first choice should be a course of doxycycline, 100 mg twice daily for seven days (level Ⅲ, grade B)[28].

Treatment failure

A repeated course or a longer course (10-14 d) with doxycycline or a macrolide has been suggested, but evidence is lacking (level Ⅳ)[26]. The most common reason for therapy failure is reinfection from an untreated partner (level Ⅱ)[26,29]. An interesting suggestion is the combined use of rifampicin and a macrolide[30]. Finally, the potential of Ct to develop antimicrobial resistance has not been well studied, although some case reports suggest resistance as a cause of treatment failure[31,32].

FIELDS TO BE DISCUSSED

Although there is a consensus about first line treatment regimens, future studies are needed in cases of treatment failure or infection persistence. 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[33]. 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[33]. 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[33]. The authors, however, concluded that the conditions of *in vitro* susceptibility studies are incompatible with the infection as it occurs *in vivo,* even although it may be useful to include investigations for antibiotic susceptibility in every patient prior to treatment[33].

NEW ACQUISITIONS FROM RCTS

A recent prospective, randomized and open-label study by Cai *et al*[19] of 221 patients affected by chronic prostatitis due to Ct infection who had received oral prulifloxacin 600 mg once daily for 14 d or doxycycline 100 mg orally twice daily for 21 d found that prulifloxacin was equivalent to the standard therapy. Moreover, in this study the authors showed that prulifloxacin was superior to standard therapy in microbiological efficacy rates in terms of mucosal IgA and interleukin-8 (IL)-8 levels decreasing[19]. This effect is probably due to an anti-inflammatory effect of quinolones.

Role of IL-8 evaluation in management of Ct infections

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 diagnosis but also in management and therapy control[12,19,34]. Several reports, moreover, suggested that IL-8 evaluation should be used, not only as a Ct infection marker, but also as a marker of therapy efficacy[12,19]. The role of molecular markers in the management of Ct infections is, therefore, clinically useful and suggested. Mazzoli *et al*[12] recently demonstrated that patients with a higher mean value for IL-8 and massive presence of mucosal IgA had evidence of 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. Moreover, in clinical practice, Cai *et al*[19] 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.

Role of IgA evaluation in management of Ct infections

Some authors demonstrated in an animal model that high production of IgA in genital tract secretions seems to be 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[34]. Particularly, the presence of chronic infection in patients affected by Ct infection has been well correlated with the presence of high levels of anti-heat shock protein 60 (anti-HSP60) and major outer membrane prottein-P2 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[35].

THERAPY OF THE INFECTION SEQUELAE

It is well known that chronic prostatitis due to Ct infection not only decreases the quality of life[36] but also has a significant impact on a couple's reproductive health[9]. Indeed, Ct has a significant role in male infertility and eradication of the infection is critical to the recovery of the man's fertility[37]. However, eradication of the infection after antibiotic therapy does not always result in recovery of semen quality and other compounds are consequently needed. Recently, Cai *et al*[38], 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. The enhanced quality of spermatozoa from an infertile status to a normal fertility index was determined through two mechanisms. The anti-inflammatory and antioxidative effects of ginseng improved the shape and concentration of spermatozoa[39] and L-arginine, L-carnitine and acetyl-L-carnitine enhanced sperm motility and function by stimulating the activity of endothelial nitric oxide synthase[40]. Two important aspects in the treatment of male infertility in patients affected by chronic prostatitis and oligoasthenoteratozoospermia due to Ct infection should be discussed. Firstly, treatment should be started concurrently with the antibiotic treatment. Then, 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[38]. Recently, Miyashita *et al*[41] demonstrated the efficacy of a new-generation fluoroquinolone, sitafloxacin, against Ct infection. Its antimicrobial activity is unique compared to conventional fluoroquinolones, although few clinical studies have been reported[42,43]. In a recent study, the microbiological eradication rates of Ct, M. genitalium and U. urealyticum were 100% (33 of 33), 100% (11 of 11) and 80% (8 of 10), respectively[44]. Even although 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.

FUTURE PROMISES BY VACCINES

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[45,46]. Moreover, the pathogenesis of Ct has not been completely elucidated and the role of host immunology is unclear[46]. Several chlamydial vaccine trials have used the major outer membrane protein as a vaccine candidate[46]. However, studies using the major outer membrane protein have been inconclusive and immunity is generally short-lived[46].

CONCLUSION

Clinical trials continue to demonstrate equivalent efficacy and tolerability of azithromycin and doxycycline regimens, and both are still recommended as first line therapy, even although some experiences with other antibiotics have been published with promising results. Further evaluation of chlamydial etiology of prostatitis and infertility is required to make a definitive statement on the association between isolation of this organism and the diseases. Finally, clinical trials should be planned in order to evaluate the real frequency of Ct resistance to standard therapy.

PILLS TO TAKE HOME

Ct infection is one of the most prevalent sexually transmitted bacterial infections worldwide.

Chronic prostatitis due to Ct infection has a significant impact on young male fertility.

First line treatment includes azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice a day for 7 d.

IL-8 evaluation should be used as a marker of therapy efficacy.

A treatment schedule with prulifloxacin 600 mg once daily for 14 d is equivalent to the standard therapy in terms of microbiological eradication but is superior over standard therapy in terms of IL-8 levels decreasing.

Phytotherapeutic agents are able to improve semen parameters in patients with chronic prostatitis and oligoasthenoteratozoospermia due to Ct infection when administered together with antibiotic treatment.

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