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Guideline

AAUS guideline for chlamydial urethritis

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ABSTRACT

Urogenital chlamydial infection is the most common sexually transmitted infection. Many cases of chlamydial infection are reported worldwide every year. Genital chlamydial infection in women can also cause obstetric issues, including infertility and miscarriage. For that purpose, appropriate care should be conducted with the latest knowledge.

Only few guidelines come from Asian countries. The Asian Association of Urinary Tract Infection and Sexually Transmitted Infection (AAUS) belonging to the Urological Association of Asia (UAA) had developed the guidelines regarding chlamydial urethritis. We have collected the feedback and updated the guidelines which is now submitted for consideration of publication. In addition to the levels of evidence, the recommendation grades were defined using the modified GRADE methodology. Herein, we present the new edition of the UAA-AAUS guidelines for chlamydial urethritis.

1. Executive summary

1.1. Diagnostic method

Microbiological diagnosis was done using specimens of first void urine.

- Nucleic acid amplification test (GR: A)
  1. Transcription mediated amplification (Hologic)
  2. Strand displacement amplification (Becton Dickinson)
  3. Polymerase chain reaction and hybridization (Greiner Bio-One)
  4. Real time polymerase chain reaction (Roche, Abbott, Seegene, Cepheid, Bio-Rad)
  5. Quenching probe polymerase chain reaction (Toyobo)
  6. Transcription reverse-transcription concerted reaction (Tosoh)
- Enzyme immunoassay (GR: C)

1.2. Treatment regimen

- Recommended treatment regimen (GR: A)
  1. Azithromycin 1g once a day
  2. Doxycycline 100 mg twice a day for 7 days
- Alternative treatment regimen (GR: B)
  1. Clarithromycin 200 mg twice a day for 7 days
  2. Ofloxacin 200 mg thrice a day for 7 days
  3. Levofloxacin 500 mg once a day for 7 days
  4. Tosufloxacin 150 mg twice a day for 7 days
  5. Sitafloxacin 100 mg twice a day for 7 days
  6. Minocycline 100 mg twice a day for 7 days
- Cure testing to detect therapeutic failure is considered 3–4 weeks after completing therapy. (GR: B)

2. Introduction (overview)

Urogenital chlamydial infection is the most common sexually transmitted infection. *Chlamydia trachomatis* causes urethritis, uterus cervicitis, pharyngeal infection and proctitis. Many cases of chlamydial infection are reported worldwide every year. Genital chlamydial infection in women can also cause obstetric issues, including infertility and miscarriage. It is thus important to reduce the number of patients with

Abbreviations: AAUS, Asian Association of Urinary Tract Infection and Sexually Transmitted Infection; NAATs, Nucleic acid amplification tests; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention; EB, elementary bodies; RB, reticulate bodies; PCR, polymerase chain reaction; TMA, transcription-mediated amplification; SDA, strand displacement amplification; EIA, Enzyme immunoassay.

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chlamydial infection. For that purpose, appropriate care should be conducted with the latest knowledge.

3. Method

We searched the literature regarding chlamydial urethritis available in PubMed and also considered other relevant publications up to 2020. We used the terms *Chlamydia trachomatis* and urethritis combined with the terms; diagnosis, evaluation, management, and treatment, for the search strategy. For the purpose of this review a total of 59 eligible publications screened by title and abstract were included in the analysis.

Level of evidence and grade of guideline recommendation was made according to the following strategy [1–3].

Type of evidence.

1a Evidence obtained from meta-analysis of randomized trials
1b Evidence obtained from at least one randomized trial
2a Evidence obtained from one well-designed controlled study without randomization
2b Evidence obtained from at least one other type of well-designed quasi-experimental study
3 Evidence obtained from well-designed nonexperimental studies (e.g., comparative studies, correlation studies, and case reports)
4 Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Recommendation grade:

A high
B moderate
C low
D very low

4. Epidemiology

According to the WHO, the estimated numbers of patients with chlamydial infection were 131 million and 127 million worldwide in 2012 and 2016, respectively [4,5] (LE: 3). The estimated pooled global prevalence of chlamydial infection in 15-49-year-old men was 2.7% (95% UI: 1.9–3.7), with regional values ranging from 1.2 to 4.0% [5] (LE: 3).

According to the CDC, the rates of reported cases of chlamydial infection were highest among adolescents and young adults aged 15–24 years during the period from 2014 through 2018 (Sexually Transmitted Disease Surveillance 2018. Available at: https://www.cdc.gov/std/stats18/default.htm.) (LE: 3). In 2017, the rate among 15-19-year-old men was 924.5 cases per 100,000 and the rate among those aged 20–24 years was 1705.4 cases per 100,000. In 2018, the rate among 15-19-year-old males was 959.4 cases per 100,000 and for those aged 20–24 years it was 1784.5 cases per 100,000.

5. Pathogen

Chlamydial urogenital infection is commonly caused by the urogenital biovar (serovars D-K) of *C. trachomatis*. *C. trachomatis* is a strict intracellular pathogen [6]. In chlamydial infection, elementary bodies (EB) infect target cells. After entering the host cell, they transform into reticulate bodies (RB) to grow and divide within a membrane-bound, host-derived parasitophorous vacuole called an inclusion. Once a critical number of bacteria has been reached, the RB transform back into EB. These are released and can then infect other target cells. Chlamydial appropriation and exploitation of the host cell machinery during invasion, inclusion formation and development are fundamental to success. However, these processes and intermediates trigger proinflammatory signaling pathways that drive innate cell influx of cytokines and chemokines such as IL-17, IK-12, IFN-ϒ, and iNOS, and activin release [7–10] (LE: 3).

6. Clinical presentation

C. trachomatis causes trachoma, severe follicular conjunctivitis [11,12] (LE: 3), and can also infect columnar epithelial cells of the urethra, uterus cervix, pharynx [13–15] and rectum [16,17] (LE: 3) as well. Genital chlamydial infections include urethritis and acute epididymitis [18,19]in men, and cervicitis and pelvic inflammatory disease [20,21] in women. In addition, pharyngeal infection and proctitis can also occur as extragenital chlamydial infections.

C. trachomatis generally infects through sexual intercourse. Genital chlamydial infection mainly causes mild subjective symptoms or lacks them. Genital infections due to *C. trachomatis* are asymptomatic in about 50% of men [22,23] (LE: 3). The rate of positive results was 4–5% in a screening test of *C. trachomatis* for asymptomatic men in their 20s [24] (LE: 3). Therefore, the chance to visit clinics is easily missed, and genital chlamydial infection remains an untreated source of infection. The incubation period is variable but is typically 1–3 weeks [18,23] (LE: 3). However, given the relatively slow replication cycle of the organism, symptoms may not appear until several weeks after exposure in those persons who develop symptoms. When men have symptoms, they may present with a mucoid or watery urethral discharge, and complain of dysuria. Their discharge may be scanty, clear, or only observed after milking the urethra.

In men, *C. trachomatis* generally accounts for about half of the causative pathogens of non-gonococcal urethritis. In 20–30% of the cases with gonococcal urethritis, *C. trachomatis* also infects simultaneously [25,26] (LE: 3). There is no strong evidence that *C. trachomatis* causes infertility in men. However, it has been associated with male subfertility and infertility [27–29] due to damage in the epithelia cells involved in spermatogenesis or apoptosis of spermatozoa caused by chlamydial lipopolysaccharide. (LE: 3).

In women, *C. trachomatis* is the predominant pathogen of sexually transmitted infections worldwide. Genital chlamydial infection in women often causes pelvic inflammatory disease followed by obstetric issues, including infertility and miscarriage [20,21,30] (LE: 3). Therefore, women with genital chlamydial infection are exposed to a possible threat to reproductive health.

7. Diagnosis

Microbiological diagnosis was done using specimens of first void urine for men and cervical swabs for women. Nucleic acid amplification tests (NAATs) (GR: A), including real-time polymerase chain reaction (real-time PCR) [31–36] (LE: 2b), transcription-mediated amplification (TMA) (LE: 2b), strand displacement amplification (SDA) [37] (LE: 2b), quenching probe polymerase chain reaction (QProbe PCR) [38] (LE: 3), PCR and hybridization [39] (LE: 3), transcription reverse-transcription concerted reaction (TRC) [40] (LE: 3) are currently the most suitable examinations because of their high sensitivity and specificity to detect *C. trachomatis*.

The downsides of NAATs are time and cost. Although NAAT-based diagnostics often requires a second visit of patients, the QProbe PCR of Toyobo and Xpert™ assay of Cepheid are commercially available rapid NAATs that can provide point-of-care testing of individual samples in approximately 90 min [38,41] (LE: 3) (GR: C).

Enzyme immunoassay (EIA) can be useful for countries in which it is impossible to put NAATs to practical use [42,43] (LE: 3) (GR: C). EIA is less sensitive to detect *C. trachomatis* than NAATs but can detect *C. trachomatis* if adequate EB exist in first void urine. In addition, there is a useful EIA that detects *C. trachomatis* within 30 min for rapid diagnosis.

8. Treatment

8.1. Antimicrobial susceptibility of C. trachomatis in vitro

Some macrolides [44,45] (LE: 2a), fluoroquinolones [46–49] (LE: 2a) and tetracyclines [49,50] (LE: 2a) have anti-chlamydial activities, and can be chosen for standard treatment regimens. Penicillin, cephalosporin, and aminoglycoside have less anti-chlamydial activity than the standard treatment regimen. Therefore, they should not be used for treatment.

Fortunately, there have been few drug-resistant *C. trachomatis* strains reported from Europe and United States [51] (LE: 3). Taking possible resistant strains into consideration may be unnecessary in most clinical and practical situations. As a result of nationwide surveillance of *C. trachomatis* antimicrobial susceptibility in Japan, the minimal inhibitory concentrations (MIC90) of ciprofloxacin, levofloxacin, tosufloxacin, sitafloxacin, doxycycline, minocycline, erythromycin, clarithromycin, azithromycin, and solithromycin were shown to be 2, 0.5, 0.25, 0.063, 0.125, 0.125, 0.25, 0.031, 0.125, and 0.008 μg/ml, respectively [52]. This surveillance project did not identify any strains resistant to fluoroquinolone, tetracycline, or macrolide agents, and concluded that antimicrobial susceptibilities were not significantly different from those previously reported [49,52].

8.2. Clinical studies for C. trachomatis urethritis

According to previous systematic reviews [53,54] (LE: 1a), azithromycin and doxycycline are appropriate for treatment (GR: A). A meta-analysis that evaluated data from randomized clinical trials of azithromycin versus doxycycline for treating urogenital chlamydial infections concluded that doxycycline had a 7% increased efficacy in the treatment of symptomatic urethral infections in men [53]. A Cochrane systematic review reported that the risk of microbiological failure was higher in the azithromycin group (risk ratio: 2.45; 95% confidence interval [CI]: 1.36–4.41); however, the clinical failure rate was not established (risk ratio: 0.94; 95% CI: 0.43–2.05).

A randomized trial reported that the microbiologic cure rate for rectal chlamydial infections was 100% with doxycycline and 74% with azithromycin [55]. An observational study showed that treatment failure for oropharyngeal chlamydial infections occurred in 8 of 78 patients (10%) treated with azithromycin and 1 of 64 (2%) treated with doxycycline, and concluded that doxycycline might be more efficacious than azithromycin [56]. Thus, concern exists regarding the effectiveness of azithromycin for concomitant rectal and/or oropharyngeal chlamydial infections.

Other antimicrobial agents (clarithromycin, levofloxacin, tosufloxacin sitafloxacin and minocycline) are appropriate as alternative treatments according to guidelines. (Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines, 2021. available at: https://www.cdc.gov/std/treatment-guidelines/chlamydia.htm. and WHO guidelines for the treatment of *Chlamydia trachomatis*. available at: https://apps.who.int/iris/bitstream/handle/10665/246165/9789241549714-eng.pdf; jsessionid = 85E146CE8D841C084418469E73714CF6?sequence = 1.) (GR: B). A previous report indicated that the microbiologic and clinical cure rates for levofloxacin were both 94% [46], and 97.2% and 88.2% for sitafloxacin, respectively [47].

8.3. Recommendation for C. trachomatis urethritis

There was high quality evidence for efficacies of azithromycin and doxycycline (LE: 1a). Although the differences are also trivial with the other medicines, the evidence is lower quality (LE: 2a). Thus, these are therefore provided as alternatives.

Azithromycin (1 g once daily) and doxycycline (100 mg twice daily) for 7 days are recommended as treatment regimens (GR: A) for *C. trachomatis* urethritis. Clarithromycin (200 mg twice daily for 7 days), ofloxacin (200 mg 3 times daily for 7 days), levofloxacin (500 mg once daily for 7 days), tosufloxacin (150 mg twice daily for 7 days), sitafloxacin (100 mg twice daily for 7 days), and minocycline (100 mg twice a day for 7 days) are recommended as alternative treatment regimens (GR: B) for *C. trachomatis* urethritis.

Cure testing to detect therapeutic failure is considered 3–4 weeks after completing therapy [57] (LE: 2) (GR: B). It was reported that of the 35 subjects with *C. trachomatis* strains genotyped at enrollment and follow-up, 7 (20%) had the same ompA sequence at both visits, whereas 28 (80%) had discordant sequences [58]. Posttreatment infections do not result only from treatment failure but also from reinfection (LE: 3) (GR: C).

9. Management of asymptomatic men whose female sexual partner is diagnosed with genital chlamydial infection

If asymptomatic men have pyuria, *C. trachomatis* is detected by NAATs in most men. If they do not have pyuria, *C. trachomatis* is detected in 20–30% of men [59] (LE: 2). In principle, treatment should be done for men who are positive for *C. trachomatis*; however, treatment for all men visiting the clinic must be conducted if the couple has a problem about violent and/or psychological discord.

10. Conclusions

Urogenital chlamydial infections are the most common sexually transmitted infections. Indeed, an enormous number of chlamydial infections are reported worldwide every year. Genital chlamydial infections in women can also result in complications, including infertility and pregnancy loss. Given the relatively slow replication cycle of *chlamydia trachomatis*, symptoms may not emerge. NAATs are recommended for diagnosis using first-void urine specimens. Fortunately, antimicrobial susceptibilities were not significantly different from those previously reported. Azithromycin or doxycycline is recommended as the treatment regimen. A test-of-cure is performed 3–4 weeks after completing therapy to identify treatment failures.

ICMJE statement for authorship

All authors meet the ICMJE authorship criteria. Y. Hiyama was responsible for the acquisition of data, the analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be submitted.

S. Takahashi and M. Yasuda were responsible for the conception and design of the study, revising it critically for important intellectual content, and final approval of the version to be submitted.

Declaration of competing interest

Satoshi Takahashi received speaker honoraria from MSD Inc., commission fee from Nippon Professional Baseball Organization and Japan Professional Football League, research grants from Abbott Japan Inc., Fujirebio Inc. and Roche Diagnostics Inc., and scholarship contribution from Shino-Test Corporation Inc.

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