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Guideline

UAA-AAUS guideline for *M. genitalium* and non-chlamydial non-gonococcal urethritis☆

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ABSTRACT

Non-chlamydial non-gonococcal urethritis (NCNGU) is defined as urethritis with neither *Neisseria gonorrhoeae* nor *Chlamydia trachomatis*. Possible causative agents of NCNGU include *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis*, *Trichomonas vaginalis*, and so on. Among these microorganisms, the pathogenicity of *M. genitalium* and *T. vaginalis* to the male urethra has been confirmed so far.

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 NCNGU and the present guidelines were updated from previous edition. Relevant references were meticulously reviewed again and latest studies were collected. 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 *M. genitalium* and non-chlamydial non-gonococcal urethritis.

1. Introduction (overview)

Urethritis is classified as either gonococcal urethritis or NGU according to the presence or absence of *Neisseria gonorrhoeae*. NGU where *Chlamydia trachomatis* is detected by any diagnostic methods is defined as "chlamydial urethritis", while the absence of *C. trachomatis* from NGU is defined as "NCNGU". Possible causative agents of NCNGU include *Mycoplasma genitalium*, *Trichomonas vaginalis*, *Ureaplasma urealyticum*, *Ureaplasma parvum*, *Mycoplasma hominis*, *Neisseria meningitidis*, *Gardnerella vaginalis*, *Haemophilus* species, herpes simplex virus, and adenovirus [1–17]. Among these, the pathogenicity of *M. genitalium* and *T. vaginalis* to the male urethra has been confirmed [16–19]. While *U. urealyticum* can cause male urethritis, there is not sufficient evidence for it as a pathogen of male urethritis [20]. In this guidelines, diagnosis and treatment recommendations for male urethritis caused by either *M. genitalium*, or *T. vaginalis* are described. In addition, the treatments for NGU are described since tests to detect NGU-related microorganisms are not available in many countries.

The levels of evidence levels (LE) of cited articles were determined according to the Outline for Preparation of Guidelines established by the Centre for Evidence-Based Medicine, Oxford [21]. The modified GRADE methodology [22] was used for grading the recommendations.

Abbreviations: AAUS, Asian Association of Urinary Tract Infection and Sexually Transmitted Infection; FVU, first voided urine; MRM, macrolide-resistance mutation; NAATs, nucleic acid amplification tests; NCNGU, non-chlamydial non-gonococcal urethritis; NGU, non-gonococcal urethritis; PCR, polymerase chain reaction; TMA, transcription mediated amplification; UAA, Urological Association of Asia.

☆ All authors meet the ICMJE authorship criteria.

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1.1. Level of evidence

1a: Systematic reviews (with homogeneity) of randomized controlled trials
1b: Randomized controlled trials
1c: All or none randomized controlled trials
2a: Systematic reviews of cohort studies
2b: Individual cohort study or low quality randomized controlled trials
2c: "Outcomes" Research; ecological studies
3a: Systematic review of case-control studies
3b: Individual case-control study
4: Case-series
5: Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Recommendation grade:

A: high;
B: moderate;
C: low
D: very low

1.2. Executive summary

- Urethritis that occurs in the absence of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* is called NCNGU.
- Several microorganisms including bacteria, viruses, or protozoa are thought to be associated with NCNGU, but only *Mycoplasma genitalium* (LE-1b, RG-A) and *Trichomonas vaginalis* (LE-2a, RG-B) have been confirmed as pathogens for male urethritis.
- *M. genitalium* is detected from urine specimens in 10–25% of male patients with symptomatic urethritis by NAATs (LE-1b, RG-A).
- *T. vaginalis* can be detected by either microscopic examination or NAATs in the urine specimens of patients with urethral symptoms or whose sexual partners are infected with *T. vaginalis* (LE-2a, RG-B).
- At the *moment*, either doxycycline regimen such as 100 mg twice a day for 7 days or azithromycin regimens, including a single 1 g oral dose of azithromycin or an extended azithromycin regimen such as 500 mg on day 1 followed by 250 mg once per day on days 2-5 are recommended as the first line treatment for *M. genitalium* urethritis (LE-3a, RG-C). Because macrolide-resistance in *M. genitalium* is spreading worldwide, in some countries where the detecting rates of MRM in *M. genitalium* are high, azithromycin regimen may not be appropriate for *M. genitalium* urethritis for much longer.
- For macrolide-resistant *M. genitalium* strains, newer fluoroquinolone regimens such as moxifloxacin 400 mg per day for 10 days (LE-3a, RG-C) or sitafloxacin 100 mg twice a day for 7 days (LE-3a, RG-C) are recommended as the second line therapies.
- For *T. vaginalis* urethritis, a single dose of either metronidazole 2 g orally or tinidazole 2 g is recommended (LE-1b, RG-A). If these regimens fail, metronidazole 500 mg twice a day for 7 days is recommended (LE-3, RG-B).
- *Ureaplasma urealyticum* can cause male urethritis, but there is not sufficient evidence to confirm it as a pathogen of male urethritis (LE-3a, RG-C). The associations of other microorganisms with male urethritis such as *Ureaplasma parvum*, *Mycoplasma hominis*, *Neisseria meningitidis,* and others remain unclear (LE-4, RG-C).

2. Pathogenicity of microorganisms for NCNGU and epidemiology

Several studies have investigated the frequency of microorganisms that are detected in NCNGU patients' urine [1–17]. *M. genitalium* is detected in 10–25% of patients with symptomatic urethritis by NAATs, but only 1–7% of asymptomatic patients at sexually transmitted infection clinics or with other infections. To determine the pathogenicity of *M. genitalium* to the male urethra, Taylor-Robinson proposed a modification to the Henle-Koch postulates that focused on epidemiological studies, animal model studies, *in vitro* antimicrobial susceptibility testing, clinical responses to antimicrobials, and transmissibility to determine the pathogenicity of *M. genitalium* to the male urethra [23]. Many studies supported the pathogenicity of *M. genitalium* to the male urethra, and it has been finally confirmed that *M. genitalium* is one of the pathogens that cause male urethritis [18,19,24–26]. However, the relationship between *M. genitalium* and prostatitis, epididymitis, and other male disorders is still unclear.

T. vaginalis is detected in the urine of 1–20% of urethritis patients by either microscopic examination or NAATs [6,9–13,15,27–31]. *T. vaginalis* is usually detected in patients whose sexual partners have trichomonal vaginitis, and most male patients are asymptomatic. However, *T. vaginalis* is also detected in patients with urethral symptoms such as urethral discomfort or dysuria, or who failed to respond to antimicrobial urethritis therapies [30]. The pathogenicity of *T. vaginalis* to the male urethra is thought to be confirmed [16,19].

U. urealyticum has been detected in 7–33% of urine specimens from symptomatic urethritis patients using NAATs [3,4,9,14,15,28,29,32–37]. The possibility that *U. urealyticum* is a pathogen of the male urethritis has long been discussed. *U. urealyticum* alone can sometimes be detected from urine specimen of patients with strong urethritis symptoms and urethritis by *U. urealyticum* can be treated with antimicrobials which are sensitive to *U. urealyticum in vitro*. However, *U. urealyticum* is also detected in asymptomatic men at higher rates [14,38]. *U. urealyticum* can be a pathogen for male urethritis, but there are still unresolved problems as described above [20].

Other microorganisms such as herpes simplex virus, adenovirus, or *N. meningitis* are also possible NCNGU pathogens [1,17]. However, comparative studies between patients with urethritis and controls have not been performed to determine the pathogenicity of these microorganisms. *U. parvum* and *M. hominis* have also been detected in the urine of urethritis patients, but are also detected in controls at high rates so the pathogenicity of these bacterial species has not been determined.

3. Diagnosis

M. genitalium can only be detected by NAATs. In some Asian countries and Australia, commercial-based tests using either multiplex-PCR or TMA on FVU are available for detection of *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*, *U. urealyticum*, *T. vaginalis*, and other bacteria [26,39–42]. *T. vaginalis* can also be detected as actively motile organisms in the urinary sediments of FVU, urethral discharge, or prostate secretions with microscopy [43]. Direct immunofluorescent antibody staining or culturing is also available. Recently, commercial-based NAATs for detecting *M. genitalium* and *T. vaginalis* have become available in some Asian countries [40], but not in all countries [25,26,31,43].

4. Treatment

4.1. Treatment for M. genitalium urethritis

4.1.1. Antimicrobial susceptibility of M. genitalium in vitro

Since the isolation of *M. genitalium* from clinical specimens is difficult, there are not many strains available for testing antimicrobial susceptibilities [44–47]. Macrolides, tetracyclines, or fluoroquinolones have been thought to have activities against *M. genitalium*. Among these antimicrobials, macrolides such as azithromycin, clarithromycin, and erythromycin have stronger antimicrobial activity against *M. genitalium* than either fluoroquinolones or tetracyclines [44,46,47]. The activities

of fluoroquinolones such as moxifloxacin and sitafloxacin are stronger than other fluoroquinolones such as norfloxacin, ciprofloxacin, and levofloxacin. However, antimicrobial-resistant *M. genitalium* strains have emerged; macrolide-resistant strains in particular are spreading worldwide [29,45–58]. Macrolide-resistant strains have been isolated from *M. genitalium* urethritis patients in Australia [45,49], Northern Europe [45,46], and Japan [47]. The macrolide-resistance in *M, genitalium* is strongly associated with point mutations of 23S rRNA, and the detection of these mutations in *M. genitalium* DNA from urine specimens has been reported from many countries. The prevalence of these MRM among *M. genitalium* genomes from clinical specimens is high: 68–79% in Australia [54–56,58], 72% in Japan [53], 48% in the USA [48,51], and 42% in Denmark [52]. It is interesting that according to a European report, the prevalence of MRM in *M. genitalium* genomes is high in countries where macrolides are recommended as a first line treatment for NGU, but significantly lower in countries where tetracycline is recommended [59]. Regarding fluoroquinolone-resistance, some studies demonstrated that treatment-failure cases by moxifloxacin [46,47,50,54,56,57,60,61] or sitafloxacin are increasing [47,62,63]. Additionally, mutations on the *gyrA* and *parC* genes, which are related to fluoroquinolone resistance in some bacteria, have been observed [47,50,53,57,62]. Furthermore, multi-drug resistant (both macrolides and fluoroquinolones) *M. genitalium* clinical strains have been isolated [46,47].

4.1.2. Clinical studies of M. genitalium urethritis

More than 30 clinical trials on *M. genitalium* urethritis, including double-blind, randomized, control studies, comparative studies, single-arm studies, and retrospective observational studies, have been reported. Between macrolides and tetracyclines, the microbiological efficacy of macrolide-regimens such as a single 1 g oral dose of azithromycin or the extended-azithromycin regimen (500 mg on day 1 followed by 250 mg once per day on days 2-5) [55,64] was superior to that of tetracycline-regimens such as doxycycline 100 mg twice a day for 7 days [18,48,65,66]. However, the efficacy of macrolides is decreasing due to the emergence of macrolide-resistant *M. genitalium* strains [29,48,50–52,54]. Some macrolide-resistant strains with MRM have emerged following the single-dose, 1 g azithromycin treatment; it is possible that azithromycin itself can induce or select for macrolide resistance [45]. The effect of azithromycin should be monitored. Thus, in some countries, tetracycline regimens such as doxycycline 200 mg/day for 7 days are recommended in place of macrolide regimens as the first line treatment for NGU, including *M. genitalium* urethritis [59].

Among the fluoroquinolones, levofloxacin efficacy was low [67,68]. However, both moxifloxacin 400 mg per day for 7-10 days and sitafloxacin 100 mg twice a day for 7 days had good efficacy against *M. genitalium* urethritis [49,63,64]. Moxifloxacin was an especially effective therapy for cases where azithromycin-treatment failed [45,49]. In Asia, sitafloxacin is available only in Japan and Thailand, but there is little evidence for its effectiveness in cases with azithromycin-treatment failure. Nevertheless, more attention should be paid to fluoroquinolone-resistant *M. genitalium*.

In some area where multi-drug resistant *M. genitalium* has emerged [46,47], antimicrobial sequential therapy should be considered. A new clinical trial has been reported from Australia [56,58], where a high-precision test was used to detect *M. genitalium* and MRM in NGU patients following treatment with doxycycline 100 mg twice daily for 7 days. MRM-negative *M. genitalium* cases were then treated with azithromycin (1 g followed by 500 mg daily for 3 days), while MRM-positive *M. genitalium* cases were treated with sitafloxacin 100 mg twice daily for 7 days. The microbiological outcomes of MRM-positive and MRM-negative cases were 92.2% and 94.8%, respectively. Recent report showed that the efficacies of either sitafloxacin 100 mg twice daily for 7 days or of moxifloxacin 400 mg once a day for 7 days were similar for MRM-positive *M. genitalium* cases [57].

4.2. Treatment regimens for trichomonal urethritis

4.2.1. Antimicrobial susceptibility of T. vaginalis in vitro

Nitroimidazoles (metronidazole and tinidazole) are the only drugs recommended for treating trichomoniasis. However, nitroimidazole-resistant strains have emerged from cases of persistent or recurrent trichomoniasis. Metronidazole resistance was found in 4–10% of cases of trichomoniasis vaginitis, and tinidazole resistance was found in 1% of cases in the USA [69,70].

4.2.2. Clinical studies for T. vaginalis urethritis

Clinical studies for trichomoniasis were performed using metronidazole or tinidazole between the 1970s and the 1990s [19,71–73]. A single 2 g oral dose of either metronidazole or tinidazole was effective with cure rates of 84–98% and 92–100%, respectively. For metroimidazole-resistant strains in single-dose metronidazole or tinidazole treatment-failure cases, an alternative regimen, such as metronidazole 500 mg orally twice a day for 7 days, is recommended [19,74].

4.3. Treatment regimens for NGU

The main NGU pathogen is *C. trachomatis*, for which azithromycin (e.g., a single 1 g dose orally) or tetracycline regimens, such as doxycycline 100 mg twice a day for 7 days, are recommended. While the microbiological efficacy of the doxycycline regimen for *M. genitalium* is lower, the efficacy of azithromycin against *M. genitalium* has decreased [29,48,75]. In this sense, the efficacies of azithromycin and doxycycline against *M. genitalium* are almost similar. Therefore, either an azithromycin regimen or a doxycycline regimen is also recommended for NGU as the first line therapy. If either *M. genitalium* or *T. vaginalis* is detected by any methods, the appropriate treatment regimen for each pathogen is recommended; however, if the first line therapy was ineffective, fluoroquinolone regimens such as moxifloxacin 400 mg a day for 7-10 days are recommended as the second line. If available, a sitafloxacin regimen, such as 100 mg twice a day for 7 days, is also recommended.

5. Recommendations for *M. genitalium* urethritis, *T. vaginalis* urethritis, or NGU treatment

5.1. M. genitalium urethritis

At the moment, either doxycycline regimen such as 100 mg twice a day for 7 days nor azithromycin regimens, including a single 1 g oral dose of azithromycin or an extended azithromycin regimen such as 500 mg on day 1 followed by 250 mg once per day on days 2–5 are recommended as the first line treatment for *M. genitalium* urethritis (LE-3a, RG-C). Because macrolide-resistance in *M. genitalium* is spreading worldwide, in some countries such as USA, Australia, Northern Europe, Japan and others, where the detecting rates of MRM in *M. genitalium* are high, azithromycin regimen may not be appropriate for *M. genitalium* urethritis for much longer. If these regimens were ineffective, a moxifloxacin regimen such as 400 mg orally once a day for 7–10 days is recommended. A sitafloxacin regimen, such as 100 mg twice a day for 7 days, is also recommended if available.

If the detecting tests of MRMs in *M. genitalium* are available, the sequential therapy such as doxycycline 100 mg twice a day for 7 days at the first visit for NGU and additional fluoroquinolone regimens such as moxifloxacin or sitafloxacin for MRM-positive cases or azithromycin regimens for MRM-negative cases is recommended.

5.2. T. vaginalis urethritis

If *T. vaginalis* is detected in urine specimens from patients with either symptomatic urethritis or asymptomatic patients whose partners have trichomoniasis vaginitis, metronidazole or tinidazole as a single 2 g dose orally is recommended. If the single-dose regimen fails, oral

metronidazole at 500 mg twice a day for 7 days is recommended.

5.3. NGU

For NGU (or chlamydial urethritis), a tetracycline regimen such as doxycycline 100 mg twice a day for 7 days or an azithromycin regimen such as a single 1 g oral dose of azithromycin is recommended. If one of these fails, regimens for *M. genitalium* or *T. vaginalis* are recommended.

6. Conclusion

M. genitalium and *T. vaginalis* are confirmed to be pathogens for NCNGU. *M. genitalium* is detected from urine specimens in 10–25% of male patients with symptomatic urethritis by NAATs. Macrolide-resistance in *M. genitalium* is spreading worldwide. Clinical efficacies of either tetracycline or macrolide regimens are similar at the moment and these regimens are recommended as the first line treatment. If these regimens are failed, fluoroquinolone regimens as moxifloxacin or sitafloxacin are the second line treatment. *T. vaginalis* can be detected by either microscopic examination or NAATs in the urine specimens. For *T. vaginalis* urethritis, a single dose of either metronidazole or tinidazole regimens are recommended.

ICMJE statement

Contributors K. Wada and R. Hamasuna reviewed the relevant references and updated the guidelines. R. Hamasuna was the supervisor. K. Wada wrote the draft of the manuscript and T. Sadahira and M. Araki reviewed it. R. Hamasuna reviewed and approved the final manuscript, and is responsible for corresponding the manuscript. S. Yamamoto was responsible for the project, updating and publishing the guidelines. All authors contributed to the writing of the final manuscript.

Declaration of competing interest

R. Hamasuna had collaborative studies with Hologic Japan Inc. Tokyo Japan or Daiichi Sankyo RD Novare Co. Ltd, Tokyo Japan.

References

[1] Bradshaw CS, Tabrizi SN, Read TR, Garland SM, Hopkins CA, Moss LM, et al. Etiologies of nongonococcal urethritis: bacteria, viruses, and the association with orogenital exposure. J Infect Dis 2006;193:336–45.
[2] Hamasuna R, Tsukino H. Urethritis. In: Naber KG, Scheffer AJ, Heyns CF, Matsumoto T, Shoskes DA, Bjerklund Johansen TE, editors. Urological Infections. Stockholm: European Association of Urology; 2010. p. 777–829.
[3] Dupin N, Bijaoui G, Schwarzinger M, Ernault P, Gerhardt P, Jdid R, et al. Detection and quantification of Mycoplasma genitalium in male patients with urethritis. Clin Infect Dis 2003;37:602–5.
[4] Deguchi T, Yoshida T, Miyazawa T, Yasuda M, Tamaki M, Ishiko H, et al. Association of Ureaplasma urealyticum (biovar 2) with nongonococcal urethritis. Sex Transm Dis 2004;31:192–5.
[5] Schlicht MJ, Lovrich SD, Sartin JS, Karpinsky P, Callister SM, Agger WA. High prevalence of genital mycoplasmas among sexually active young adults with urethritis or cervicitis symptoms in La Crosse, Wisconsin. J Clin Microbiol 2004;42:4636–40.
[6] Sturm PD, Moodley P, Khan N, Ebrahim S, Govender K, Connolly C, et al. Aetiology of male urethritis in patients recruited from a population with a high HIV prevalence. Int J Antimicrob Agents 2004;24(Suppl 1):S8–14.
[7] Leung A, Eastick K, Haddon LE, Horn CK, Ahuja D, Horner PJ. Mycoplasma genitalium is associated with symptomatic urethritis. Int J STD AIDS 2006;17:285–8.
[8] Lewis DA, Pillay C, Mohlamonyane O, Vezi A, Mbabela S, Mzaidume Y, et al. The burden of asymptomatic sexually transmitted infections among men in Carletonville, South Africa: implications for syndromic management. Sex Transm Infect 2008;84:371–6.
[9] Lewis DA, Chirwa TF, Msimang VM, Radebe FM, Kamb ML, Firnhaber CS. Urethritis/cervicitis pathogen prevalence and associated risk factors among asymptomatic HIV-infected patients in South Africa. Sex Transm Dis 2012;39:531–6.
[10] Gaydos C, Maldeis NE, Hardick A, Hardick J, Quinn TC. Mycoplasma genitalium compared to chlamydia, gonorrhoea and trichomonas as an aetiological agent of urethritis in men attending STD clinics. Sex Transm Infect 2009;85:438–40.
[11] Black V, Magooa P, Radebe F, Myers M, Pillay CLewis DA. The detection of urethritis pathogens among patients with the male urethritis syndrome, genital ulcer syndrome and HIV voluntary counselling and testing clients: should South Africa's syndromic management approach be revised? Sex Transm Infect 2008;84:254–8.
[12] Stamm WE, Batteiger BE, McCormack WM, Totten PA, Sternlicht A, Kivel NM. A randomized, double-blind study comparing single-dose Rifalazil with single-dose azithromycin for the empirical treatment of nongonococcal urethritis in men. Sex Transm Dis 2007;34:545–52.
[13] Le Roux MC, Ramoncha MR, Adam A, Hoosen AA. Aetiological agents of urethritis in symptomatic South African men attending a family practice. Int J STD AIDS 2010;21:477–81.
[14] Wetmore CM, Manhart LE, Lowens MS, Golden MR, Jensen NL, Astete SG, et al. Ureaplasma urealyticum is associated with nongonococcal urethritis among men with fewer lifetime sexual partners: a case-control study. J Infect Dis 2011;204:1274–82.
[15] Kim SJ, Lee DS, Lee SJ. The prevalence and clinical significance of urethritis and cervicitis in asymptomatic people by use of multiplex polymerase chain reaction. Kor J Urol 2011;52:703–8.
[16] Sena AC, Bachmann LH, Hobbs MM. Persistent and recurrent Trichomonas vaginalis infections: epidemiology, treatment and management considerations. Expert Rev Anti Infect Ther 2014;12:673–85.
[17] Ito S, Hanaoka N, Shimuta K, Seike K, Tsuchiya T, Yasuda M, et al. Male non-gonococcal urethritis: from microbiological etiologies to demographic and clinical features. Int J Urol 2016;23:325–31.
[18] Taylor-Robinson D, Jensen JS. Mycoplasma genitalium: from Chrysalis to multicolored butterfly. Clin Microbiol Rev 2011;24:498–514.
[19] Workowski KA, Bolan GA, Centers for Disease CPrevention. Sexually transmitted diseases treatment guidelines. MMWR Recomm Rep (Morb Mortal Wkly Rep) 2015;64:1–137. 2015.
[20] Horner P, Donders G, Cusini M, Gomberg M, Jensen JS, Unemo M. Should we be testing for urogenital Mycoplasma hominis, Ureaplasma parvum and Ureaplasma urealyticum in men and women? - a position statement from the European STI Guidelines Editorial Board. J Eur Acad Dermatol Venereol 2018;32:1845–51.
[21] Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ, et al. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995–8.
[22] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
[23] Taylor-Robinson D. The role of mycoplasmas in non-gonococcal urethritis: a review. Yale J Biol Med 1983;56:537–43.
[24] Jensen JS. Mycoplasma genitalium infections. Dan Med Bull 2006;53:1–27.
[25] Sethi S, Singh G, Samanta PSharma M. Mycoplasma genitalium: an emerging sexually transmitted pathogen. Indian J Med Res 2012;136:942–55.
[26] Hamasuna R. Mycoplasma genitalium in male urethritis: diagnosis and treatment in Japan. Int J Urol 2013;20:676–84.
[27] Wetmore CM, Manhart LE, Lowens MS, Golden MR, Whittington WL, Xet-Mull AM, et al. Demographic, behavioral, and clinical characteristics of men with nongonococcal urethritis differ by etiology: a case-comparison study. Sex Transm Dis 2011;38:180–6.
[28] Sena AC, Lensing S, Rompalo A, Taylor SN, Martin DH, Lopez LM, et al. Chlamydia trachomatis, Mycoplasma genitalium, and Trichomonas vaginalis infections in men with nongonococcal urethritis: predictors and persistence after therapy. J Infect Dis 2012;206:357–65.
[29] Manhart LE, Gillespie CW, Lowens MS, Khosropour CM, Colombara DV, Golden MR, et al. Standard treatment regimens for nongonococcal urethritis have similar but declining cure rates: a randomized controlled trial. Clin Infect Dis 2013;56:934–42.
[30] Schwebke JR, Hook 3rd EW. High rates of Trichomonas vaginalis among men attending a sexually transmitted diseases clinic: implications for screening and urethritis management. J Infect Dis 2003;188:465–8.
[31] Munson KL, Napierala M, Munson E, Schell RF, Kramme T, Miller C, et al. Screening of male patients for Trichomonas vaginalis with transcription-mediated amplification in a community with a high prevalence of sexually transmitted infection. J Clin Microbiol 2013;51:101–4.
[32] Yokoi S, Maeda S, Kubota Y, Tamaki M, Mizutani K, Yasuda M, et al. The role of Mycoplasma genitalium and Ureaplasma urealyticum biovar 2 in postgonococcal urethritis. Clin Infect Dis 2007;45:866–71.
[33] Lee SR, Chung JM, Kim YG. Rapid one step detection of pathogenic bacteria in urine with sexually transmitted disease (STD) and prostatitis patient by multiplex PCR assay (mPCR). J Microbiol 2007;45:453–9.
[34] Berntsson M, Lowhagen GB, Bergstrom T, Dubicanac L, Welinder-Olsson C, Alvengren G, et al. Viral and bacterial aetiologies of male urethritis: findings of a high prevalence of Epstein-Barr virus. Int J STD AIDS 2010;21:191–4.
[35] Shigehara K, Kawaguchi S, Sasagawa T, Furubayashi K, Shimamura M, Maeda Y, et al. Prevalence of genital Mycoplasma, Ureaplasma, Gardnerella, and human papillomavirus in Japanese men with urethritis, and risk factors for detection of urethral human papillomavirus infection. J Infect Chemother 2011;17:487–92.
[36] Kawaguchi S, Shigehara K, Sasagawa T, Shimamura M, Nakashima T, Sugimoto K, et al. Liquid-based urine cytology as a tool for detection of human papillomavirus, Mycoplasma spp., and Ureaplasma spp. in men. J Clin Microbiol 2012;50:401–6.
[37] Carne CA, Gibbs J, Delaney A, Sonnex C, Verlander NQ, Smielewska A, et al. Prevalence, clinical features and quantification of genital non-viral infections. Int J STD AIDS 2013;24:273–7.
[38] Yu JT, Tang WY, Lau KH, Chong LY, Lo KK. Asymptomatic urethral infection in male sexually transmitted disease clinic attendees. Int J STD AIDS 2008;19:155–8.

[39] Yoshida T, Ishiko H, Yasuda M, Takahashi Y, Nomura Y, Kubota Y, et al. Polymerase chain reaction-based subtyping of ureaplasma parvum and ureaplasma urealyticum in first-pass urine samples from men with or without urethritis. Sex Transm Dis 2005;32:454–7.
[40] Choe HS, Lee DS, Lee SJ, Hong SH, Park DC, Lee MK, et al. Performance of Anyplex II multiplex real-time PCR for the diagnosis of seven sexually transmitted infections: comparison with currently available methods. Int J Infect Dis 2013;17: e1134–40.
[41] Takanashi M, Ito S, Kaneto H, Tanahashi Y, Kitanohara M, Yanagihara A, et al. Development and clinical application of an InvaderPlus(R) assay for the detection of genital mycoplasmas. J Infect Chemother 2015;21:516–9.
[42] Tabrizi SN, Costa AM, Su J, Lowe P, Bradshaw CS, Fairley CK, et al. Evaluation of the hologic panther transcription-mediated amplification assay for detection of Mycoplasma genitalium. J Clin Microbiol 2016;54:2201–3.
[43] Hobbs MM, Sena AC. Modern diagnosis of Trichomonas vaginalis infection. Sex Transm Infect 2013;89:434–8.
[44] Hamasuna R, Jensen JS, Osada Y. Antimicrobial susceptibilities of Mycoplasma genitalium strains examined by broth dilution and quantitative PCR. Antimicrob Agents Chemother 2009;53:4938–9.
[45] Jensen JS, Bradshaw CS, Tabrizi SN, Fairley CK, Hamasuna R. Azithromycin treatment failure in Mycoplasma genitalium-positive patients with nongonococcal urethritis is associated with induced macrolide resistance. Clin Infect Dis 2008;47: 1546–53.
[46] Jensen JS, Fernandes P, Unemo M. In vitro activity of the new fluoroketolide solithromycin (CEM-101) against macrolide-resistant and -susceptible Mycoplasma genitalium strains. Antimicrob Agents Chemother 2014;58:3151–6.
[47] Hamasuna R, Le PT, Kutsuna S, Furubayashi K, Matsumoto M, Ohmagari N, et al. Mutations in ParC and GyrA of moxifloxacin-resistant and susceptible Mycoplasma genitalium strains. PloS One 2018;13:e0198355.
[48] Schwebke JR, Rompalo A, Taylor S, Sena AC, Martin DH, Lopez LM, et al. Re-evaluating the treatment of nongonococcal urethritis: emphasizing emerging pathogens–a randomized clinical trial. Clin Infect Dis 2011;52:163–70.
[49] Bradshaw CS, Jensen JS, Tabrizi SN, Read TR, Garland SM, Hopkins CA, et al. Azithromycin failure in Mycoplasma genitalium urethritis. Emerg Infect Dis 2006; 12:1149–52.
[50] Tagg KA, Jeoffreys NJ, Couldwell DL, Donald JA, Gilbert GL. Fluoroquinolone and macrolide resistance-associated mutations in Mycoplasma genitalium. J Clin Microbiol 2013;51:2245–9.
[51] Getman D, Jiang A, O'Donnell M, Cohen S. Mycoplasma genitalium prevalence, coinfection, and macrolide antibiotic resistance frequency in a multicenter clinical study cohort in the United States. J Clin Microbiol 2016;54:2278–83.
[52] Salado-Rasmussen KJensen JS. Mycoplasma genitalium testing pattern and macrolide resistance: a Danish nationwide retrospective survey. Clin Infect Dis 2014;59:24–30.
[53] Deguchi T, Ito S, Yasuda M, Sato Y, Uchida C, Sawamura M, et al. Surveillance of the prevalence of macrolide and/or fluoroquinolone resistance-associated mutations in Mycoplasma genitalium in Japan. J Infect Chemother 2018;24:861–7.
[54] Bissessor M, Tabrizi SN, Twin J, Abdo H, Fairley CK, Chen MY, et al. Macrolide resistance and azithromycin failure in a Mycoplasma genitalium-infected cohort and response of azithromycin failures to alternative antibiotic regimens. Clin Infect Dis 2015;60:1228–36.
[55] Couldwell DL, Lewis DA. Mycoplasma genitalium infection: current treatment options, therapeutic failure, and resistance-associated mutations. Infect Drug Resist 2015;8:147–61.
[56] Read TRH, Fairley CK, Murray GL, Jensen JS, Danielewski J, Worthington K, et al. Outcomes of resistance-guided sequential treatment of Mycoplasma genitalium infections: a prospective evaluation. Clin Infect Dis 2019;68:554–60.
[57] Murray GL, Bodiyabadu K, Danielewski J, Garland SM, Machalek DA, Fairley CK, et al. Moxifloxacin and sitafloxacin treatment failure in Mycoplasma genitalium infection: association with parC mutation G248T (S83I) and concurrent gyrA mutations. J Infect Dis 2020;221:1017–24.
[58] Su JP, Tan LY, Garland SM, Tabrizi SN, Mokany E, Walker S, et al. Evaluation of the SpeeDx Resistance Plus MG diagnostic test for Mycoplasma genitalium on the applied biosystems 7500 fast quantitative PCR platform. J Clin Microbiol 2018;56.
[59] Unemo M, Salado-Rasmussen K, Hansen M, Olsen AO, Falk M, Golparian D, et al. Clinical and analytical evaluation of the new Aptima Mycoplasma genitalium assay, with data on M. genitalium prevalence and antimicrobial resistance in M. genitalium in Denmark, Norway and Sweden in 2016. Clin Microbiol Infect 2018; 24:533–9.
[60] Shimada Y, Deguchi T, Yamaguchi Y, Yasuda M, Nakane K, Yokoi S, et al. gyrB and parE mutations in urinary Mycoplasma genitalium DNA from men with non-gonococcal urethritis. Int J Antimicrob Agents 2010;36:477–8.
[61] Couldwell DL, Tagg KA, Jeoffreys NJ, Gilbert GL. Failure of moxifloxacin treatment in Mycoplasma genitalium infections due to macrolide and fluoroquinolone resistance. Int J STD AIDS 2013;24:822–8.
[62] Deguchi T, Ito S, Yasuda M, Kondo H, Yamada Y, Nakane K, et al. Emergence of Mycoplasma genitalium with clinically significant fluoroquinolone resistance conferred by amino acid changes both in GyrA and ParC in Japan. J Infect Chemother 2017;23:648–50.
[63] Takahashi S, Hamasuna R, Yasuda M, Ito S, Ito K, Kawai S, et al. Clinical efficacy of sitafloxacin 100 mg twice daily for 7 days for patients with non-gonococcal urethritis. J Infect Chemother 2013;19:941–5.
[64] Jernberg E, Moghaddam A, Moi H. Azithromycin and moxifloxacin for microbiological cure of Mycoplasma genitalium infection: an open study. Int J STD AIDS 2008;19:676–9.
[65] Mena LA, Mroczkowski TF, Nsuami M, Martin DH. A randomized comparison of azithromycin and doxycycline for the treatment of Mycoplasma genitalium-positive urethritis in men. Clin Infect Dis 2009;48:1649–54.
[66] Bradshaw CS, Jensen JS, Waites KB. New horizons in Mycoplasma genitalium treatment. J Infect Dis 2017;216:S412–9.
[67] Maeda SI, Tamaki M, Kojima K, Yoshida T, Ishiko H, Yasuda M, et al. Association of Mycoplasma genitalium persistence in the urethra with recurrence of nongonococcal urethritis. Sex Transm Dis 2001;28:472–6.
[68] Takahashi S, Ichihara K, Hashimoto J, Kurimura Y, Iwasawa A, Hayashi K, et al. Clinical efficacy of levofloxacin 500 mg once daily for 7 days for patients with non-gonococcal urethritis. J Infect Chemother 2011;17:392–6.
[69] Kirkcaldy RD, Augostini P, Asbel LE, Bernstein KT, Kerani RP, Mettenbrink CJ, et al. Trichomonas vaginalis antimicrobial drug resistance in 6 US cities, STD Surveillance Network, 2009-2010. Emerg Infect Dis 2012;18:939–43.
[70] Schwebke JR, Barrientes FJ. Prevalence of Trichomonas vaginalis isolates with resistance to metronidazole and tinidazole. Antimicrob Agents Chemother 2006; 50:4209–10.
[71] Spence MR, Harwell TS, Davies MC, Smith JL. The minimum single oral metronidazole dose for treating trichomoniasis: a randomized, blinded study. Obstet Gynecol 1997;89:699–703.
[72] Thin RN, Symonds MA, Booker R, Cook S, Langlet F. Double-blind comparison of a single dose and a five-day course of metronidazole in the treatment of trichomoniasis. Br J Vener Dis 1979;55:354–6.
[73] Mati JK, Wallace RJ. The treatment of trichomonal vaginitis using a single dose of tinidazole by mouth. East Afr Med J 1974;51:883–8.
[74] Bosserman EA, Helms DJ, Mosure DJ, Secor WE, Workowski KA. Utility of antimicrobial susceptibility testing in Trichomonas vaginalis-infected women with clinical treatment failure. Sex Transm Dis 2011;38:983–7.
[75] Khosropour CM, Manhart LE, Colombara DV, Gillespie CW, Lowens MS, Totten PA, et al. Suboptimal adherence to doxycycline and treatment outcomes among men with non-gonococcal urethritis: a prospective cohort study. Sex Transm Infect 2014;90:3–7.