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Guideline

The JAID/JSC guidelines to Clinical Management of Infectious Disease 2017 concerning male urethritis and related disorders

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1. Introduction

Sexually transmitted infections (STIs) are infectious diseases transmitted by sexual activities in the broad sense. Common STIs are urethritis in males and cervicitis in females. STIs also include diseases that cause skin lesions around the genitalia such as genital herpes, syphilis, condyloma acuminatum, and phthiriasis pubis. In addition, causative agents of STIs have recently been detected also in extragenital areas such as the rectum, pharynx, and conjunctiva due to increased diversity of sexual practice including oral sex and occasionally cause symptoms. Urethritis and cervicitis are frequently caused by *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, and gonococcal urethritis and cervicitis and chlamydial urethritis and cervicitis have been used as terms to indicate these conditions. Recently, the concept of urethritis and cervicitis caused by microorganisms other than *N. gonorrhoeae* and *C. trachomatis* has been recognized. Particularly, in males, the term non-chlamydial non-gonococcal urethritis has begun to be used for conditions in which neither gonococcus nor chlamydia is detected. Among such agents, the pathogenicity of *Mycoplasma genitalium* has been demonstrated [1]. Many patients with male urethritis exhibit severe symptoms and are often initiated to treat at the initial visit. Moreover, the percentage of gonococcal strains that are resistant to many kinds of antibiotics is increasing. Therefore, guidelines that can recommend drugs that are likely to cure these diseases are necessary.

The Japanese Association for Infectious Disease (JAID) and the Japanese Society of Chemotherapy (JSC) published the JAID/JSC Guide to Clinical Management of Infectious Disease 2011 in 2012, and a revised version in 2014 [2]. The treatments for STIs were summarized in these guides. However, it is difficult to show recommendation grades and evidence level of the literature concerning all such treatments in the guides. Here, this guideline for the diagnosis and treatment are presented with comments by focusing on male urethritis, which is the most frequent male STI and requires early treatment. Concerning the diagnosis and treatment for STIs, guidelines have been published by the Japanese Society for Sexually Transmitted Infections (JSSTI) [3], and this text has been prepared with maximum consistency with the JSSTI guidelines. However, it should be noted that there are some differences in matters including the selection of drugs concerning the items that have been newly clarified such as drug susceptibility of causative microorganisms of STIs.

Supplementary notes:

The recommendation grades and evidence levels of the literature were determined according to the Outline for the Preparation of the Guidelines to Clinical Management of Infectious Disease established by JAID/JSC. While the materials cited as evidence were

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selected primarily from the Japanese literature, the recommendation grades were evaluated comprehensively also by reviewing the overseas literature.

- Recommendation grades
  - A: Strongly recommended
  - B: General recommendation
  - C: Comprehensive evaluation by the attending physician
- Evidence levels
  - I: Randomized controlled study
  - II: Non-randomized controlled study
  - III: Case report
  - IV: Specialist's opinion

2. Male urethritis

[Executive summary]

- Urethritis is a disease that presents primarily with pain on urination and urethral discharge. It is classified into gonococcal and non-gonococcal depending on the causative microorganism (I, A). Non-gonococcal urethritis in which chlamydia is detected is called chlamydial urethritis, and urethritis in which neither gonococcus nor chlamydia is detected is called non-chlamydial non-gonococcal urethritis (I, B).
- On the first diagnosis, it is desirable to judge whether the condition is gonococcal or non-gonococcal by confirming the presence or absence of gonococcus, a Gram-negative (diplo) coccus, according to the results of Gram staining of urethral discharge or urinary sediment (I, A). If microscopy for gonococci is impossible, the nucleic acid amplification tests (NAATs) are examined using first-catch urine. *N. gonorrhoeae* and *C. trachomatis* should be tested simultaneously (I, B).
- Details of the diagnosis and treatment according to the causative microorganisms are shown in the sections of gonococcal and chlamydial urethritis. Moreover, details of urethritis in which neither *N. gonorrhoeae* nor *C. trachomatis* is detected are described as non-chlamydial non-gonococcal urethritis.
- During treatment, sexual contacts not using the condom must be avoided, and the partners should be examined and treated simultaneously (I, A).

2.1. Comments

The disease presenting primarily with pain on urination and urethral discharge is called urethritis. It mostly occurs as an STI, but symptoms of urethritis may also be caused by common bacteria, drugs, or mechanical stimulation, and such conditions are distinguished from STI. Urethritis is often caused as the causative microorganism attaches to the mucosa of the navicular fossa located slightly inside the urethral meatus and proliferates there. Urethritis is the most frequent male an STI. In Japan, the incidence of urethritis increased from around 1990 and began to decrease after a peak around 2002 but has leveled out since around 2009 [4–6].

Urethritis is classified into gonococcal and non-gonococcal urethritis depending on detection or no detection of gonococcus. Non-gonococcal urethritis in which *C. trachomatis* is detected is called chlamydial urethritis, and others are called non-chlamydial non-gonococcal urethritis. *Trichomonas vaginalis* is occasionally detected, when the condition is called trichomonal urethritis. Many microbial species may be involved in non-chlamydial non-gonococcal urethritis as causative microorganisms [7–11]. Among them, studies have established the urethral pathogenicity of *M. genitalium* [1,12–18] (I, A). However, while tests for detection of this microorganism are available, its clinical use is not approved by the health insurance system of Japan, and it is presently used for research purposes alone. The involvement of other microorganisms is described in the section of non-chlamydial non-gonococcal urethritis. In gonococcal urethritis, chlamydia is detected simultaneously in 20–30% of the patients [8,13,19] (I, B). While the frequency of detection of causative microorganisms in male urethritis varied with the year and region in which the examination was performed, *C. trachomatis* has been detected most frequently in Japan, followed by *N. gonorrhoeae* and *M. genitalium* [10,11].

Symptoms of urethritis differ between gonococcal and non-gonococcal urethritis. In gonococcal urethritis, symptoms appear 3–7 days after infection. The patient complains of intense urethral pain and pain on urination and shows reddening around the urethral meatus. There is copious urethral discharge, which is yellowish white and purulent. In non-gonococcal urethritis, symptoms appear 1–3 weeks after infection. Urethral pain and pain on urination are milder, and many patients complain of discomfort, itching, and a feeling of strangeness of the urethra. Urethral discharge is often small in amount and serous [20] (III, B). However, symptoms vary individually, and there are mild cases of even gonococcal urethritis and cases of non-gonococcal urethritis that present with severe symptoms as in gonococcal urethritis. Also, about 50% of patients are considered asymptomatic despite detection of *C. trachomatis* [21–23] (III, B). Particularly, caution is necessary for male partners of patients with chlamydial cervicitis as they may be asymptomatic [23,24] (III, B).

The diagnosis of urethritis is based on symptoms of urethritis and demonstration of urethral inflammation, in principle [3]. Urethral inflammation is confirmed by checking the presence or absence of leukocytes by an elastase test of first-catch urine, in the sediment of first-catch urine or on the urethral smear. Pyuria is judged to be positive when the leukocyte count is $\geq$ 5/high power field (hpf) under microscopy at $\times$400 ($\geq$10/hpf according to the CDC Guidelines) [13]. It is also judged to be positive when 2 or more leukocytes are detected on microscopy at $\times$1000 with oil immersion in Gram-stained urethral smear. In addition, detection of Gram-negative diplococci in urethral discharge or sediment of first-catch urine should be confirmed. While gonococci can also be detected by simple staining, differentiation from other cocci is necessary. If gonococci are detected by microscopic examination, it is recommended to send the urethral discharge for culture and drug susceptibility testing. Moreover, NAATs are performed using first-catch urine to detect *C. trachomatis* (Table 1). If gonococci are not demonstrated on microscopy, NAATs are performed using first-catch urine for both *N. gonorrhoeae* and *C. trachomatis*. If urethral inflammation cannot be established despite symptoms of urethritis, it is desirable to perform NAAT to detect both *N. gonorrhoeae* or *C. trachomatis*. In partners of patients with chlamydial cervicitis, NAAT should be performed to detect *C. trachomatis* even when symptoms of urethritis or urethral inflammation cannot be confirmed [24]. Among other microorganisms, *T. vaginalis* and *M. genitalium* also cause non-chlamydial non-gonococcal urethritis, but this is described later.

Urethritis may develop into epididymitis, and it is caused by *N. gonorrhoeae* or *C. trachhomatis*. *M. genitalium* may also be isolated from urine specimens of patients with epididymitis, but further accumulation of cases is necessary to confirm that it is a causative microorganism of epididymitis [1,25,26]. Primary symptoms of epididymitis are fever (often high fever) accompanied by enlargement and tenderness of the scrotal contents. They are often accompanied by symptoms of urethritis.

In urethritis patients, *N. gonorrhoeae* and *C. trachomatis* may be simultaneously detected in the pharynx [27–39] (II, A). If such

Table 1
Nucleic acid amplification tests available in Japan for *N. gnorrhoeae* and *C. trachomatis*

Nucleic acid amplification test	Transcription mediated amplification (TMA)	Strand displacement amplification (SDA)	TaqMan PCR	Real-time PCR	QProbe	TRC
Product name	Aptima™ Combo2 Chlamydia/Gonorrhea	BD ProbeTec™ ET Chlamydia trachomatis Neisseria gonorrhoeae	Cobas® 4800 System CT/NG	AccuGENE™ m-CT/NG	GENECUBE® Neisseria gonorrhoeae Chlamydia trachomatis	TRCReadyR CT/NG
Distributor	Hologic Japan	Becton, Dickinson and Company Japan	Roche Diagnostics	Abbott Japan	Toyobo	Tosoh Bioscience
Sample types	First-catch urine, male urethral swab, cervical swab, pharyngeal swab, gargle fluid	First-catch urine, male urethral swab, cervical swab, pharyngeal swab	First-catch urine, cervical swab, gargle fluid	First-catch urine, male urethral swab, cervical swab, vaginal swab	Male first-catch urine, cervical swab	Urethral swab, cervical swab, pharyngeal swab, gargle fluid

microorganisms are detected in the pharynx, pharyngeal symptoms are absent in most patients. Rare cases complain pharyngeal pain and hoarseness. Both *N. gonorrhoeae* and *C. trachomatis* can be detected by NAATs [29,30,32,34,35,37–40] (II, B). Some uncertain points, such as the timing of tests remain about NAATs to evaluate the effectiveness of antibiotics for pharyngeal infection. In Japan, simultaneous testing of genital and pharyngeal samples is not covered by health insurance. In addition, causative microorganisms of STI may be detected in rectal mucosa or rectal swabs of patients who engage in anal sex [1,3,13,41] (I, A). Causative microorganisms of STIs are also detected in eye discharge, blood, ascites, arthrocentesis fluid, etc., as extragenital infections [42–47] (III, B). While it is possible to detect causative microorganisms of STIs in these samples by NAATs, these are not covered by health insurance in Japan.

The principle of management for male urethritis is to properly treat the causative microorganism. However, many patients with urethritis show poor drug compliance such as terminating treatment when symptoms are alleviated and not taking drugs as instructed and do not visit the clinic for re-examination [48]. Furthermore, there is the possibility of involvement of multiple causative agents, and they may be detected simultaneously in the pharynx or rectum as well as the urethra. Therefore, it is optimal to select a treatment that is expected to show a response rate of $\geq$95% against causative microorganisms of STIs in not only the urethra but also the pharynx and other sites by a single administration as much as possible. As described above, treatment should be initiated after confirming the presence or absence of gonococci and distinguishing gonococcal and non-gonococcal urethritis at the first visit. If the condition is mildly symptomatic or asymptomatic, treatment should be initiated after the results of tests to identify the causative microorganisms such as NAATs become available. The CDC guidelines of the US recommend a therapeutic regimen effective against both *N. gonorrhoeae* and *C. trachomatis* such as dual therapies, because patients are not expected to be examined again [13]. However, as we must manage urethritis under the Japanese health insurance system, it is desirable to first treat *N. gonorrhoeae* in gonococcal urethritis and to initiate treatment for *C. trachomatis* on the re-visit by checking the results of chlamydial tests, and we should explain the importance of re-examination to patients. In addition, as described later, CTRX 1 g is recommended as the first-line treatment for gonococcal infection in Japan [3]. Since most *N. gonorrhoeae* strains are considered to be treatable with CTRX 1g at present in Japan, dual therapies in consideration of resistant strains are not recommended unlike foreign countries. However, it must be added to discuss that the treatment may be changed depending on the state of resistance in *N. gonorrhoeae* to CTRX. In addition, prevention to spread causative microorganisms of STIs is also important as well as treatment of urethritis. Along with treatment of sexual partners, patients must be instructed to avoid sexual contacts without using the condom (including oral sex) during the treatment period [3] (IV, A).

Infection sources of male urethritis may be all men and women who have causative microorganisms for urethritis including professional women working in the sex industries, amateur women, and homosexual men. Clinicians must understand that many patients get infected by oral sex alone [21,30,32,37,39,47,49–52] (III, A).

3. Gonococcal urethritis

[Executive summary]

- Methods to detect gonococci include microscopy of Gram-stained specimens, isolation culture, and NAATs. Microscopy of Gram-stained specimens is characterized by the possibility of rapid diagnosis, isolation culture by the possibility of drug susceptibilities of *N. gonorrhoeae*, and NAATs by the possibility of simultaneous detection of *C. trachomatis* (I, A).
- Drug-resistant *N. gonorrhoeae* strains are increasing, and most antibiotics with an treatment indication for *N. gonorrhoeae* by health insurance cannot be used in actual clinical treatment. Presently, CTRX and SPCM are the only antibiotics that are covered by insurance and can be recommended as effective against gonococcal infections (II, A).
- Although gonococcal pharyngeal infection is mostly asymptomatic, it is important as an infection source (II, B). Since SPCM is poorly transported to the pharynx, the only recommendable antibiotic is CTRX (III, B).
- The partner must also be examined and treated simultaneously (I, A).

3.1. Comments

Gonococcal infection is infection due to *N. gonorrhoeae* and is a prevalent STI along with genital chlamydial infection. Human to human contact is its main route of transmission, and it primarily causes urethritis in men and cervicitis in women. It also causes epididymitis, salpingitis, pelvic inflammatory disease, disseminated gonococcal infection, pharyngeal infection, conjunctivitis, rectal infection and others. The severity of symptoms varies widely according to the site of infection, and while marked symptoms appear in urethritis and conjunctivitis, cervicitis may be asymptomatic. Pharyngeal infection and rectal infection are often asymptomatic, but patients may complain of pharyngeal pain and hoarseness in pharyngeal infection and anal discomfort, diarrhea, and purulent/mucous and bloody stools in anal infection [13].

Gonococci can be detected by microscopy of Gram-stained urethral smear, discharge or urinary sediment, culturing on selective media, and NAATs using first-catch urine or urethral swabs. Microscopic examination is the quickest way for the diagnosis [53] but cannot be recommended in rectal or pharyngeal samples, because the identification of gonococci is difficult in such samples [3,13]. With the increase in multidrug-resistant *N. gonorrhoeae*

strains, isolation culture and drug susceptibility testing should be performed as much as possible [54] (IV, B). For NAATs, TMA (APTIMA™ Combo2 Chlamydia/Gonorrhea), SDA (BD ProbeTec ET™ Chlamydia trachomatis Neisseria gonorrhoeae) [50], TaqMan PCR (Cobas® 4800 system CT/NG) [37], Realtime PCR (AccuGENE™ m-CT/NG) [55], QProbe (GENECUBE®® Neisseria gonorrhoeae) and TRC (TRCReady® CT/NG) are available in Japan (Table 1). Pharyngeal samples are collected using swabs or as gargle fluids for APTIMA™ Combo2 Chlamydia/Gonorrhea and TRCReady® CT/NG, using swabs for BD ProbeTec ET™ Chlamydia trachomatis Neisseria gonorrhoeae [50], and as gargle fluids for Cobas® 4800 system CT/NG [37]. The use of AccuGENE™ m-CT/NG and GENECUBE®® Neisseria gonorrhoeae for pharyngeal samples is not covered by Japanese health insurance.

Recently, *N. gonorrhoeae* have markedly developed resistance to antibiotics, and multidrug resistance is becoming prevalent [27,56–73] (I, A). Few isolates in Japan are susceptible to penicillin antibiotics, and the resistance rates against tetracyclines and fluoroquinolones are 70–80%. These antibiotics cannot be used unless isolated *N. gonorrhoeae* strains are confirmed to be susceptible to these antibiotics. Third generation oral cephalosporins cannot be selected for treatment, because their resistance rates are 30–50%. CFIX, which has the strongest anti-gonococcal activity among the oral cephalosporins, is effective to an extent by a regimen of 200 mg at a time, twice a day, for 1–3 days, but many cases of poor response have been reported [63–65] (II, B). Sales of CDZM, which used to be recommended, were discontinued at the end of March 2016. Therefore, antibiotics that are covered by Japanese health insurance and are consistently effective are only CTRX and SPCM. CTRX was originally administered in Japan at 1 g single dose by intravenous drip infusion. It is injected intramuscularly at 250 mg in the US and at 500–750 mg in Australia and Europe [13]. The regimen of CTRX 1g single dose has been shown to be effective against gonococci in not only the urethra but also pharynx and rectum [27,60,74–76] (II, A). SPCM is an antibiotic used by intramuscular injection. It shows a bacteriological efficacy rate of nearly 100% against gonococcal urethritis [77] (II, B). However, its effect on the pharynx has been shown to be low [78]. It is administered intramuscularly at a large dose and causes intense pain on intramuscular injection. There is a report of an increase in resistant strains in an area overseas, but nearly all strains isolated in Japan are susceptible.

In 2009, the world's first strain resistant to CTRX, which is the first-line drug for gonococcal infection, was reported in Japan [31]. This was followed by reports of 2 other resistant strains in France and Spain [79–82]. While the spread of CTRX-resistant strains has not been observed, increases in CTRX low-sensitivity strains have been reported from various parts of the world [57,83], and their trends are attracting attention (IV, B). Although AZM is recognized to be effective against gonococcal infection, there have been a number of reports of regional surveillance data indicating decreases in responses to this drug [84]. Moreover, as there have been a series of reports of *N. gonorrhoeae* strains highly resistant to AZM from foreign countries, AZM is not recommended as the first-line drug in the Japanese guidelines [67–71] (II, B). The use of AZM may be considered if the patient is allergic, or do not respond, to other recommended drugs. Among other drugs, TAZ/PIPC and MEPM have strong antibacterial activity to *N. gonorrhoeae*, but neither is covered by Japanese health insurance. While dual therapies have been reported to be effective against resistant strains [85,86], it is not recommended for gonococcal infection in Japan, where CTRX 1g is presently effective. However, it must be noted that treatments recommended for gonococcal urethritis may be changed widely as gonococci become increasingly resistant.

After treatment, patients are urged to re-visit to check the results of the chlamydia test and the effectiveness of the treatment, and, if chlamydia is positive, anti-chlamydial treatment is initiated. During the treatment, patients should be instructed to avoid sexual contacts without using the condom, and their partners should be examined and treated simultaneously.

3.2. Recommendation

3.2.1. Male gonococcal urethritis

After a latent period of 2–7 days, symptoms of urethra including copious yellowish white purulent discharge, pain on urination, hot sensation and itching of the urethra, and reddening of the urethral meatus appear. The symptoms are severer than those of non-gonococcal urethritis.

First choice

CTRX 1 g intravenous drip infusion in a single dose.

Second choice

SPCM 2 g intramuscular injection in a single dose.

3.2.2. Gonococcal epididymitis

If gonococcal urethritis is left untreated, gonococci in the urethra ascend the urethra and cause epididymitis. Epididymitis is initially unilateral but becomes bilateral without treatment and occasionally causes azoospermia after treatment. Local symptoms of inflammation are severe with enlargement of the scrotal contents and intense local pain, and patients may have difficulty in walking. They are often accompanied by systemic inflammatory symptoms such as fever and leukocytosis.

First choice

CTRX 1 g, once or twice daily, intravenous drip infusion, for over 1–7 days.

The administration period should be modified according to the severity.

Second choice

SPCM 2 g, intramuscular injection in single dose; additional administration of 2 g each in the bilateral gluteal regions with a total of 4 g after 3 days of the initial injection if the effect of the initial treatment by SPCM is insufficiency.

4. Non-gonococcal urethritis

- Urethritis in which gonococci are not detected is called non-gonococcal urethritis (I, A). Non-gonococcal urethritis in which *C. trachomatis* is detected is called chlamydial urethritis, and the rest is included in non-chlamydial non-gonococcal urethritis (I, C). If *T. vaginalis* is detected, the condition is called trichomonal urethritis.
- In Japan, of the examinations for causative microorganisms of non-gonococcal urethritis, only those for the detection of *C. trachomatis* are covered by health insurance. Therefore, non-gonococcal urethritis is treated similarly to chlamydial urethritis.
- *T. vaginalis* can be observed by microscopy of a wet mount of urinary sediment or urethral discharge.

4.1. Comments

The criterion of non-gonococcal urethritis is the urethritis without detection of *N gonorrhoeae*. The causative microorganisms include many kinds of bacteria, protozoa, fungus, virus or undetermined organisms [8,9]. In these organisms, *C. trachomatis* is detected from around 50% of patients with non-gonococcal urethritis in Japan. In addition, almost microorganisms cannot be detected by health insurance-covered tests. In this condition, we

have to treat patients with non-gonococcal urethritis by according to treatment regimen to chlamydial urethritis. If other microorganisms are detected before the treatment, patients with non-gonococcal urethritis should be treated by appropriate drugs for the detecting microorganisms. For example, *T. vaginalis* can be observed by microscopy of a wet mount of urinary sediment or urethral discharge and the patients with trichomonal urethritis should be MN, but not macrolide or tetracycline.

5. Chlamydial urethritis

[Executive summary]

- Although *C. trachomatis* is a causative microorganism of trachoma, it also infects the urethra, uterine cervix, and pharynx, which have columnar epithelium similar to that of the palpebral conjunctiva.
- Urethritis due to *C. trachomatis* infection often shows only mild symptoms such as pain on urination or passes unnoticed. Therefore, patients are not willing to visit medical institutions, and as chlamydial infection persists, they become sources of infection (IV, A).
- Male genital chlamydial infection is acquired by sexual contacts and causes urethritis and epididymitis (I, A).
- In males, chlamydial urethritis accounts for about half the cases of non-gonococcal urethritis (I, A). The frequency of mixed infection with *C. trachomatis* in gonococcal urethritis is 20–30% (I, B).
- *C. trachomatis* is susceptible to some macrolides, quinolones, and tetracyclines with anti-chlamydial activity, and resistant strains are not prevalent (I, A).

5.1. Comments

Although *C. trachomatis* is the causative microorganism of trachoma, it also infects the urethra, uterine cervix, and pharynx, which have columnar epithelium similar to that of the palpebral conjunctiva. Trachoma, which is transmitted from one eye to others through hands, decreased in Japan with improvements in the hygienic environment such as the use of disinfectants. In addition, as eye infection is easy to perceive subjectively and objectively and is easy to attract medical attention, conjunctival infection has been controlled in Japan. However, urethral and cervical infection often remains unperceived subjectively or objectively due to mildness of inflammatory symptoms such as discharge, misses opportunities of medical examination, persists over a long period, and often becomes a source of infection.

C. trachomatis primarily infects the urogenital organs, and chlamydial infection accounts for the highest percentage of all patients with STI worldwide. In males, chlamydial urethritis accounts for about a half of non-gonococcal urethritis, and mixed infection with *C. trachomatis* is observed in 20–30% of gonococcal urethritis [8,13,19] (I, B). In males, the primary site of chlamydial infection is the urethra, and urethral infection may lead to epididymitis. The pathogenicity of *C. trachomatis* to prostatitis is still controversial. Anal sex may result in proctitis. There are a large number of asymptomatic carriers in both males and females. This may be the reason for its highest prevalence among STIs.

Male chlamydial urethritis may occur 1–3 weeks after infection, and as symptoms remain unnoticed in many patients, determination of the exact time of infection is difficult. Compared with gonococcal urethritis, the latent period is longer, the onset of symptoms is slower, and symptoms tend to be milder. Discharge of male urethritis is serous and small or moderate in amount, and pain on urination is often mild. A relatively high percentage of patients may be nearly asymptomatic with only mild itching or discomfort of the urethra [20] (IV, A). On screening tests of first-catch urine in asymptomatic males in their 20s, the positive rate has been reported to be 4–5% [21,22] (III, B).

In male chlamydial urethritis, *C. trachomatis* is detected in first-catch urine samples by methods such as the IDEIA™ PCE *Chlamydia* based on EIA and the PCR, which is NAAT. The *C. trachomatis* detection kits using NAATs have high sensitivities and specificities and are recommended for appropriate diagnosis (I.A). In Japan, five NAATs are covered by health insurance: TMA assay (Aptima™ Combo2 Chlamydia/Gonorrhea), SDA assay (BD ProbeTec ET™ Chlamydia trachomatis/Neisseria gonorrhoeae) [50], TaqMan PCR (Cobas® 4800 System CT/NG) [37], Realtime PCR assay (AccuGENE™ m-CT/NG) [55], QProbe assay (GENECUBE®® Chlamydia trachomatis) and TRCReady® CT/NG (Table 1). Urethral swabs by scraping can also be used as a sample but is not recommended because of pain during sampling except for special purposes including sampling of *C. trachomatis* strains. In addition, the chlamydia antibody testing is not recommended, because it does not reflect the time of infection or therapeutic effect.

Acute epididymitis often occurs following male chlamydial urethritis, but it may also occur without clear symptoms of urethritis. Acute epididymitis in middle-aged or younger patients may be caused frequently by *C. trachomatis* [87,88] (IV, B). Chlamydial acute epididymitis often shows milder swelling, is localized in the epididymis, and causes milder fever than acute bacterial epididymitis due to other bacteria. Chlamydial acute epididymitis is diagnosed using first-catch urine similarly to chlamydial urethritis.

Of macrolide, tetracycline, and quinolone antibiotics, those with anti-chlamydial activity should be administered [58,89–95] (I, A). Other antibiotics including penicillin, cephems, and aminoglycosides are not appropriate for the treatment of chlamydial infection because of low response rates. For patients with chlamydial epididymitis exhibiting a high fever, it is recommended to perform intravenous drip infusion of a tetracycline such as MINO. After control of fever and enlargement of the scrotal contents, shift to oral MINO following injection for over a total of 14 days (IV, C).

Spread of antibiotics resistant *C. trachomatis* is not observed [94] (IV, B). However, as there are cases of treatment failure due to re-infection and insufficient oral medication, drug administration guidance is necessary.

In treating infected individuals, their partners should also be checked for chlamydial infection and make sure to be treated if found positive. Male partners of those with chlamydial cervicitis are likely to be positive for chlamydial infection if they show pyuria even when they are asymptomatic. Moreover, about 20% of those without pyuria are positive for chlamydial infection [23,24] (III, B). To avoid trouble between partners, initiating treatment before testing is justified for ensuring eradication of *C. trachomatis* [24].

It is desirable to check the response of *C. trachomatis* by methods such as NAATs and EIA 2–3 weeks after treatment and confirm cure (VI, C). The serum antibody test is not available for judgment of cure.

5.2. Recommendation

1) AZM 1000 mg orally in a single dose
2) CAM 200 mg orally twice a day for 7 days
3) MINO 100 mg orally twice a day for 7 days
4) DOXY 100 mg orally twice a day for 7 days
5) LVFX 500 mg orally once a day for 7 days
6) TFLX 150 mg orally twice a day for 7 days

7) STFX 100 mg orally twice a day for 7 days

For epididymitis with fever

MINO 100 mg at a time, twice a day, intravenous drip infusion for 3–5 days.

After control of fever and enlargement of the scrotal contents, shift to MINO 100 mg twice a day, for over a total of 14 days.

6. Non-chlamydial non-gonococcal urethritis

[Executive summary]

- Male urethritis in which neither *N. gonorrhoeae* nor *C. trachomatis* is detected is called non-chlamydial non-gonococcal urethritis (I, B).
- There is no difference in clinical picture between non-chlamydial non-gonococcal urethritis and chlamydial urethritis.
- *M. genitalium* and *T. vaginalis* are confirmed to be causative microorganisms (I, A).
- If *T. vaginalis* is detected, the condition is called trichomonal urethritis (I, A). For the detection of trichomonas, wet mounts of discharge or first-catch urine are examined under microscopy for protozoa showing wave motion.
- Examinations for causative microorganisms of non-chlamydial non-gonococcal urethritis are not covered by health insurance in Japan.
- Trichomonal urethritis is treated using oral MN (I, A).
- AZM can be used for non-chlamydial non-gonococcal urethritis, and STFX should be used for treatment-failure cases by AZM (IV, B). However, macrolide-resistant M. genitalium is increasing. However, macrolide-resistant M. genitalium is increasing.

6.1. Comments

C. trachomatis is detected in 30–50% of patients with non-gonococcal urethritis, and the condition is called chlamydial urethritis. Moreover, urethritis in which neither *N. gonorrhoeae* nor *C. trachomatis* is detected is called non-chlamydial non-gonococcal urethritis. There is no difference in clinical picture between chlamydial urethritis and non-chlamydial non-gonococcal urethritis. Some microorganisms that have pathogenicities and drug susceptibilities similar to those of *C. trachomatis* and are difficult to culture by usual methods have been speculated to be involved in non-chlamydial non-gonococcal urethritis. A large number of studies have been conducted concerning the causative microorganisms involved in non-chlamydial non-gonococcal urethritis [7–11]. Particularly, in studies using NAATs, many bacteria, viruses, and protozoal species have been detected in first-catch urine and urethral swabs [8,9]. *M. genitalium*, *T. vaginalis*, *Ureaplasma urealyticum*, *Haemophilus influenzae*, herpes simplex virus, adenovirus or others have been reported as candidate pathogens. In addition, bacteria in the oral cavity, such as *Neisseria meningitides* are occasionally isolated from urinary or urethral specimens of patients with urethritis, and these microorganisms are also candidates for possible pathogens in consideration of the recent diversity of sexual practice [96–98].

Of these microorganisms, the pathogenicity of *T. vaginalis* and *M. genitalium* has been established (I, A). *T. vaginalis* is the cause of vaginal trichomoniasis. It has also been shown by infection experiments, etc., to be pathogenic in male urethritis [99], and the frequency of male urethritis due to *T. vaginalis* has also been found to be relatively high by studies using NAATs [100]. If *T. vaginalis* is detected, urethritis is called trichomonal urethritis. Evidence concerning the pathogenicity of *M. genitalium* in urethritis has been accumulated by evaluations based on the modified Koch's postulates [1,7,8,14–18,101]: the microorganism should be detected more frequently in large number from patients with symptoms of urethritis that from those without, inoculation experiments have been carried out in humans and animals, the same microorganism is isolated again from experimental animals, and clinical and microbiological cure after treatment with an antibiotics to which the microorganism is susceptible *in vitro*. Some other microorganisms have also been shown to be likely pathogens of urethritis. *U. urealyticum* is occasionally isolated alone from symptomatic urethritis patients. Adenovirus and *N. meningitides* are also likely to be pathogenic, but controlled studies using asymptomatic males and basic researches are insufficient, and evidence to identify them as pathogens is inadequate [7,8,10,11]. However, while the pathogenicity of microorganisms detected in the urethra for male urethritis is low, treatment is occasionally necessary as some of them cause bacterial vaginitis in females.

6.2. Trichomonal urethritis

Urethritis due to *T. vaginalis* causes slight urethral pain or urethral itching, but symptoms are generally mild and often absent [3,13] (I, A). It is diagnosed by confirming protozoa showing wave motion by microscopy of wet mounts of urethral discharge or sediment of first-catch urine. The size of the protozoa is similar to that of a leukocyte and is readily observable. While *T. vaginalis* can also be detected by NAATs, the use of NAATs for *T. vaginalis* are limited to research purposes and is not covered by health insurance in Japan. *T. vaginalis* is also considered to cause prostatitis, and the protozoa living in the prostate or seminal gland is speculated to advance to the urethra and cause symptoms, but this has not been confirmed (IV, C).

6.2.1. Recommendation

MN 250 mg orally twice a day for 10 days.

According to reports from overseas, 4–10% of *T. vaginalis* strains have acquire resistance to MN, but this has not been confirmed in Japan (III, C) [102,103]. It is recommended to treat partners simultaneously, because many of them have vaginal trichomoniasis.

6.3. Non-chlamydial non-gonococcal urethritis

M. genitalium is established as a pathogen (I, A). If *T. vaginalis*is not detected, treatment should be initiated by assuming *M. genitalium* to be the pathogen. Meanwhile, microorganisms such as *U. urealyticum*, *N. meningitides*, and *H. influenza* may be the cause in some patients, and culturing of first-catch urine is occasionally helpful for the diagnosis [8] (III, C). There are also some cases suspected to be STI due to the presence of opportunities of infection but these pathogenic microorganisms are not detected despite various tests [104] (III, C). Symptoms vary widely, including serous or purulent urethral discharge, urethral pain, pain on urination, urethral discomfort, and urethral itching. Conditions that exhibit symptoms of urethritis are included in this category. Tests for these microorganisms including *M. genitalium* are not covered by health insurance in Japan except for culture tests. NAATs can be used for researches but not covered by health insurance [8].

Non-chlamydial non-gonococcal urethritis is more intractable than chlamydial urethritis and recurs in some patients even after the same treatment (**I, A**). *M. genitalium* is poorly responsive to tetracyclines and quinolones such as LVFX and is most susceptible to macrolides [105–107]. (III, A). RCTs using macrolides and tetracyclines against non-gonococcal urethritis have been conducted, resulting in demonstration of superiority of macrolides against

M. genitalium [1,15,16,108,109] (**I, B**). However, treatment failure cases using AZM, a macrolide antibiotic, were reported [110], and a strain highly resistant to macrolides was isolated from urethral samples from patients who did not respond to the AZM treatment [111]. Macrolide resistance of *M. genitalium* was shown to be closely related to mutation of domain V of 23S rRNA, the action site of macrolides [111] (II, B). The response rate to macrolides has also decreased in clinical studies [108,109,112] (I, B), and *M. genitalium* genes with macrolide-resistance associated mutations (MRAM) have been detected worldwide [113–117]. Japan is not an exception, and 40-70% of *M. genitalium* strains may be macrolide-resistant [118–120] (III, B). MFLX, classified as a respiratory quinolone, was shown to be effective against these macrolide-resistant *M. genitalium* strains [110] (II, B). Although the use of MFLX for the treatment of urethritis is not covered by health insurance in Japan, STFX has a strong antibiotic activity [105] and has shown high efficacy against *M. genitalium* in clinical studies [92,93,121] (III, B). However, treatment failures using MFLX have been reported [113,122], and *M. genitalium* strains resistant to MFLX have been detected [106] (III, B). The mechanism of MFLX resistance is being evaluated, and mutations of gyrase gene and topoisomerase IV gene are suspected to be involved, but no conclusion has been reached at present [120,121,123,124] (IV, C). However, it is reasonable to assume that multidrug-resistant *M. genitalium* resistant to macrolides and respiratory quinolones have appeared [106,107,125], (IV, B) and treatment of urethritis due to *M. genitalium* is expected to become difficult in the future.

In Japan, however, tests to detect *M. genitalium* are not covered by health insurance. Therefore, there is no choice but to treat non-gonococcal urethritis similarly to chlamydial urethritis. Despite the progressive development of AZM resistance, in consideration of the high frequency of *C. trachomatis* detection in non-gonococcal urethritis, it is recommended to initiate treatment using AZM (II, B) and to use STFX in patients who do not respond to AZM (IV, B). If *M. genitalium* has been detected by examinations at the patient's own expense, the use of STFX as the first drug is acceptable. STFX should be used at 100 mg at a time twice a day, and its efficacy may be low at lower doses. In some regions overseas, tests which can detect MRAM in *M. genitalium* are available, [126,127] and health insurance coverage of such tests will also become essential for the treatment of urethritis in Japan. If AZM or STFX are failed to eradicate *M. genitalium*, there is no choice among health insurance-covered drug for non-gonococcal urethritis in Japan. A case report showed the usefulness of SPCM and DOXY and some drugs such as pristinamicin, solithromycin, gepotidacin are under development.

U. urealyticum is susceptible to tetracyclines, macrolides, and quinolones, in this order. Although all these 3 classes are considered effective at present, the antibiotic activity is high in STFX but low in CPFX among quinolones.

Since none of the examinations to detect microorganisms in non-goococcal non-chlamydial urethritis is covered by health insurance, the judgment of cure is based on resolution of symptoms and disappearance of leukocytes from first-catch urine or normalization of the leukocytes counts in urethral smears [104,128] (III, C).

6.3.1. Recommendation

1) AZM 1000 mg orally in a single dose

For patients not responding to the above regimen or strongly suspected to be infected by *M. genitalium*.

1) STFX 100 mg orally twice a day for 7 days

If *N. meningitidis* or *H. influenzae* is detected alone on a culture test, the treatment is selected according to the results of drug susceptibility testing.

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