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GUIDELINE

# German evidence- and consensus-based guideline on the management of penile urethritis

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**Summary**

Urethritis is a common condition predominantly caused by sexually transmitted pathogens such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Mycoplasma genitalium*. It is not possible to differentiate with certainty between pathogens on the basis of clinical characteristics alone. However, empirical antibiotic therapy is often initiated in clinical practice. The aim of this clinical practice guideline is to promote an evidence-based syndrome-orientated approach to the management of male adolescents and adults with symptoms of urethritis.

Besides recommendations for the diagnosis, classification and choice of treatment, this guideline provides recommendations for the indication to empirically treat patients with penile urethritis. A novel feature compared to existing, pathogen-specific guidelines is the inclusion of a flowchart for the syndrome-orientated practical management. For suspected gonococcal urethritis requiring empirical treatment, ceftriaxone is recommended. Due to the risk of

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*Lead medical societies*:

German Dermatological Society (DDG), German STI Society (DSTIG) – Society for the Promotion of Sexual Health

*Participating societies and organizations*:

German Medical Society for Health Promotion (ÄGGF)

Professional Association of German Dermatologists (BVDD)

Federal Association of Physicians of Public Health Departments (BVÖGD)

German Association of Outpatient Physicians for Infectious Diseases and HIV Medicine (DAGNÄ)

German AIDS Service Organizations (DAH)

German AIDS Society (DAIG)

German Society of Andrology (DGA)

German Society for Hygiene and Microbiology (DGHM)

German Society of Infectious Diseases (DGI)

German Society of Internal Medicine (DGIM)

German Society of Pediatrics and Adolescent Medicine (DGKJ)

German Society for Pediatric Infectious Diseases (DGPI)

German Society for Urology (DGU)

Competence Network HIV/AIDS

Paul Ehrlich Society for Infection Therapy (PEG)

PrEP.Jetzt

Robert Koch Institute (RKI)

*Chlamydia trachomatis* co-infection, doxycycline should also be prescribed, unless follow-up for the treatment of possible co-infections is assured. For suspected non-gonococcal urethritis, doxycycline is the recommended empirical treatment. In the empiric treatment of both gonococcal and non-gonococcal penile urethritis, azithromycin is reserved for cases where doxycycline is contraindicated. This guideline also includes detailed recommendations on differential diagnosis, pathogen-specific treatments and specific situations, as well as patient counselling and follow-up.

**KEYWORDS**
chlamydia, discharge, dysuria, gonorrhea, mycoplasma, trichomonas, Urethritis

## INSTRUCTIONS FOR THE USE OF THE GUIDELINE

The present publication is focused on clinical contents of the guideline and represents a substantially shortened version of the long version. Further guideline documents including detailed and additional information are published on the pages of the AWMF: https://register.awmf.org/de/leitlinien/detail/013-099. Particular attention should be paid to the information in the chapter "Special Notes/Disclaimer" in the long version when applying the guideline recommendations. Several other chapters are only included in the long version: "Further diagnostics if no pathogen is detected", "Further diagnostics in chronic/recurrent urethritis", "Point-of-care diagnostics", "Antibiotic therapy if other mycoplasma or ureaplasma are detected", "Antibiotic therapy if *T. vaginalis* is detected", "Therapy of idiopathic urethritis". In addition, the long version includes detailed justifications and rationales for the guideline recommendations. Detailed information on the methods of guideline development and the results of systematic reviews and meta-analyses are available in the methods report and evidence report.

Recommendations of this guideline refer to individuals with male genital phenotype, irrespective of the gender assigned at birth or their gender identity.

Table 1 shows the used strengths of recommendation, symbols and their implications, modified from GRADE[1] and AWMF regulation.[2] Table 2 shows the meaning of the

**TABLE 1** Strength of recommendation: wording, symbols and implications, modified from GRADE[1] and AWMF.[2]

| Strength of recommendation | Wording | Symbol | Implications |
|---|---|---|---|
| *Strong* recommendation *for* a procedure | "… should …" | ↑↑ | *We believe that all or almost all informed people would make this decision*. Clinicians have to spend less time on the process of decision-making with the patient. |
| *Conditional* recommendation *for* a procedure | "… might …" | ↑ | *We believe that most informed people would make this decision, but a substantial part would not*. Clinicians will need to devote more time to ensure that the choice of the procedure reflects the values and preferences of individual patients. |
| *Open* recommendation | "… may be considered …" | 0 | *Currently, no recommendation in favor or against a procedure can be made due to certain conditions* (for example, lacking or insufficient evidence, unclear risk-benefit ratio). |
| *Conditional* recommendation *against* a procedure | "… might not …" | ↓ | *We believe that most informed people would make this decision, but a substantial part would not*. |
| *Strong* recommendation *against* a procedure | "… should not …" | ↓↓ | *We believe that all or almost all informed people would make this decision*. |

**TABLE 2** GRADE evaluations of the confidence in the effects estimates and their meaning, modified from Balshem et al.[223] and Meerpohl et al.[224]

| GRADE evaluation | Symbol | Meaning |
|---|---|---|
| High | ++++ | We are very confident that the true effect lies close to that of the effect estimate. |
| Moderate | +++O | We are moderately confident in the effect estimate: The true effect is likely to be close to the effect estimate, but there is a possibility that it is relevantly different. |
| Low | ++OO | Our confidence in the effect estimate is limited: The true effect may be relevantly different from the effect estimate. |
| Very low | +OOO | We have only very little confidence in the effect estimate: The true effect is likely to be relevantly different from the effect estimate. |

GRADE evaluations of the confidence in the prevalence and effect estimates.

A concise presentation of the recommendations for clinical practice is given in the flowchart (Figure 1).

## DEFINITION, EPIDEMIOLOGY, AND CLINICAL BASICS

### Definition and clinical features

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| **4.01** | Urethritis is an inflammation of the urethral mucosa. | Consensus-based statements, strong consensus (100%) |
| **4.02** | Clinically, penile urethritis is characterized by subjective symptoms (dysuria, alguria, burning, itching, and pain in the area of distal urethra and external urethral meatus) and clinical signs (urethral discharge, erythema in the area of external urethral meatus, inguinal lymphadenopathy). The symptoms and signs may occur individually or in combination and may be discreet or pronounced. A substantial proportion of urethral infections with sexually transmitted pathogens is asymptomatic. | |

### Epidemiology

Although urethritis is a common disease, only few data on the incidence of urethritis or urogenital infections in the total population of Germany are available.[3,4] For the period from 2007 to 2017, a stable incidence of urethritis over time with approximately 200 cases/year per 100,000 men aged 15 years or older was reported for France.[5]

In a survey representative for the population in Germany, the highest prevalences of urogenital infections with *Chlamydia (C.) trachomatis* were observed in women aged 18–24 with 2.3% and in men aged 25–29 with 3.5%.[6] In Europe, the incidence of infections with gonococci in men was three times higher than in women in 2019.[4] Cross-sectional studies in Germany among men who have sex with men (MSM) showed a prevalence of urogenital infections with *C. trachomatis*, *Neisseria (N.) gonorrhoeae*, and *Mycoplasma (M.) genitalium* of altogether 8%–9%.[7,8] Only 37.0% of the participants with exclusively urogenital infection reported symptoms.[8]

### Etiology and pathogen epidemiology

Urethritis can be caused by a broad spectrum of infectious pathogens including bacteria, viruses, fungi, and protozoa.[9,10] In symptomatic penile urethritis, the pathogens detected most often are *C. trachomatis*, *N. gonorrhoeae*, and *M. genitalium*, with a prevalence of 18% (95% confidence interval (CI): 15%–22%, n = 10,319, 33 publications,[11–43] GRADE ++OO), 14% (95% CI: 10%–18%, n = 10,057, 30 studies,[11,12,14,18,20,21,23–25,27–30,32,33,35–41,43–50] GRADE ++OO), and 13% (95% CI: 10%–16%, n = 5,177, 20 studies,[12,18,23,24,26,29,30,32,33,36–38,40–43,49,51–53] GRADE ++OO), respectively. In two studies including exclusively MSM, 2% (95% CI: 1%–3%, n = 490, GRADE +OOO) of those who had a urethral *C. trachomatis* infection detected had serovars of the groups L1–L3.[54,55]

It should be taken into account that pathogens for which the relevance as a cause of urethritis symptoms is either questionable or needs to be determined on an individual basis are also frequently detected, for example, *Ureaplasma* (*U.*) *urealyticum*, *U. parvum*, and *M. hominis*. While the association of urethral infection with *M. genitalium* with symptoms of urethritis has been demonstrated in multiple epidemiological studies,[32,56–69] the majority of case-control studies found no association of *U. parvum* and *M. hominis* with urethritis symptoms.[69–71] Heterogeneous study results are available for *U. urealyticum* depending on the stratification used for confounding factors.[58,69–74] For *U. urealyticum*, there is an association between high pathogen load,[58] young age,[70] and a low number of sexual partners[58] with symptomatic urethritis.[75] Based on the assessment of the guideline group, *U. parvum* and *M. hominis* should, therefore, usually be rated as commensal pathogens, while the relevance of *U. urealyticum* should be evaluated on a case-by-case basis.

Other pathogens detected less often include Haemophilus ssp., Trichomonas (T.) vaginalis, Candida ssp., Gardnerella (G.) vaginalis, N. meningitidis, Streptococcus (Str.) agalactiae, Str. pneumoniae, Staphylococcus (S.) aureus, Escherichia (E.) coli, herpes simplex virus 1 and 2, and adenoviruses. It is important to note that the causality between urethral detection and urethritis has not been established for all pathogens mentioned; this applies in particular to Str. agalactiae, Str. pneumoniae, and S. aureus.

Urethral infections with more than one pathogen are common. Notable is the prevalence of co-infections with *C. trachomatis* if *N. gonorrhoeae* is detected (21% (95% CI: 17–26%), n = 2,015, 19 studies,[11,18,27,32,33,36,38–40,43,50,76–83] GRADE ++OO). In case of urethral detection of *N. gonorrhoeae*, *C. trachomatis*, or *M. genitalium*, co-infections with at least one other of the three pathogens must generally be anticipated in approximately10%–15% of the cases, GRADE (+OOO)–(++OO).

Data on co-infections of other anatomical localizations are limited. Pharyngeal co-infections with *N. gonorrhoeae* have been observed in 19% (95% CI: 10–33%, n = 2,426, 89% MSM, 3 studies,[81,84,85] GRADE +OOO) or, if exclusively heterosexual men are considered, in 5% (95% CI: 3%–9%, n = 266 heterosexual men, 1 study,[81] GRADE). This plays an important role in therapy selection for urethral infections with *N. gonorrhoeae*; see corresponding section.

In a substantial proportion of patients with symptoms of urethritis, no cause is identified;[86] in clinical studies, the term "idiopathic urethritis" has been established.[72,86–91] The systematic reviews/meta-analyses

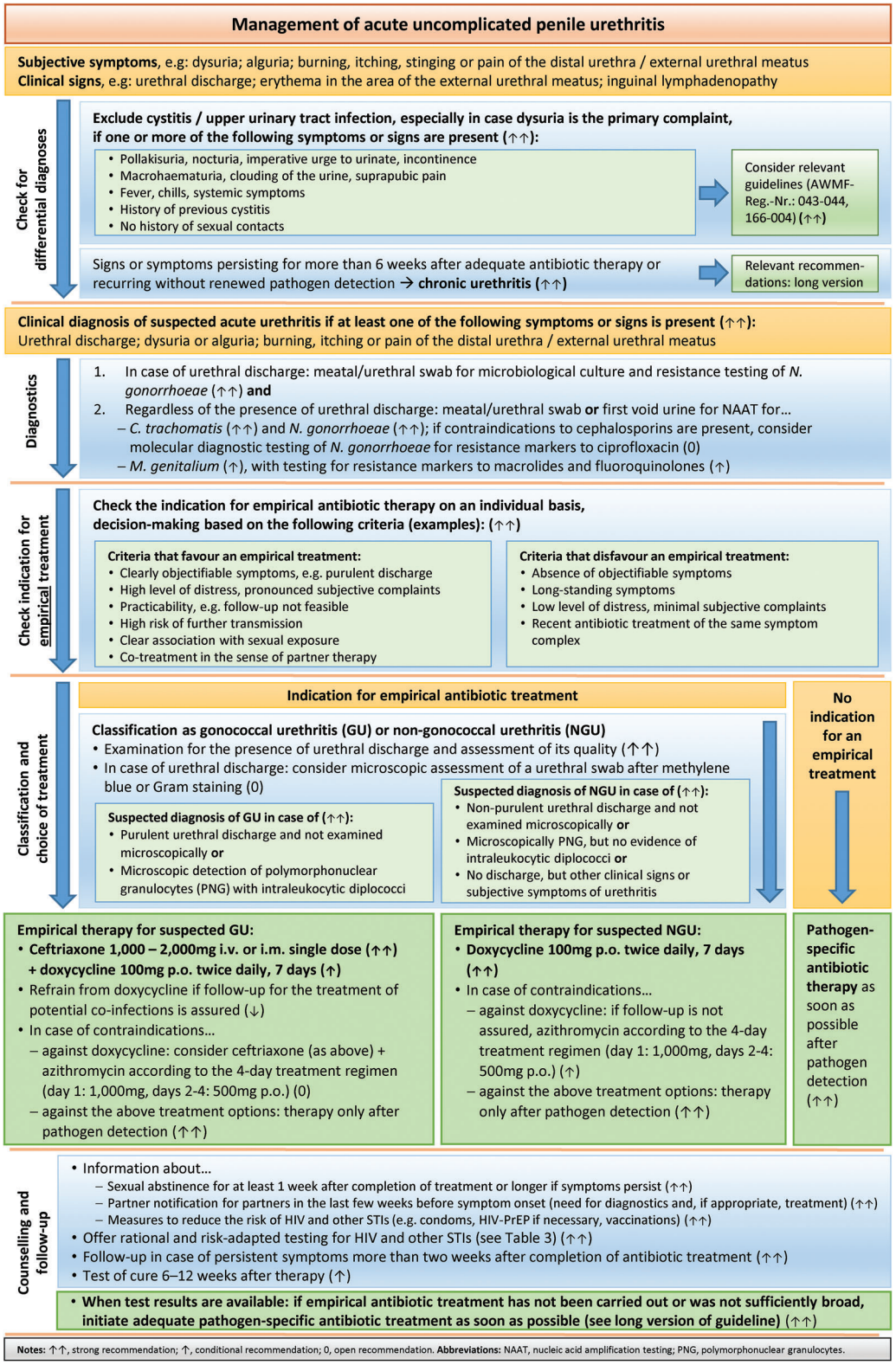


**FIGURE 1** Flowchart for the syndrome-oriented management of patients with symptoms or clinical signs of penile urethritis. Explanations: ↑↑, strong recommendation ("should"); ↑, conditional recommendation ("might"); 0, open recommendation ("may be considered").
*Abbr.*: NAAT, nucleic acid amplification testing (e.g., PCR)

revealed that in 43% (95% CI: 34%–53%, n = 6,117, 11 studies,[12,18,24,27,30,33,35,37,38,40,43] GRADE +OOO) of patients with symptoms of penile urethritis no pathogen was detected. Studies on the urethral microbiome indicate that shifts of the bacterial flora indicative of dysbiosis and infections outside the classical spectrum of pathogens might be causative for the urethritis symptoms in these cases.[88–91]

Non-infectious causes of urethritis must also be considered,[10] such as injuries[92–96] and irritant-toxic or allergic triggers.[97] However, the available data on this aspect are restricted to case reports or theoretical considerations based on clinical experience.

## INITIAL DIAGNOSIS AND DIFFERENTIAL DIAGNOSES

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| **4.03** | The clinical presumptive diagnosis of urethritis **should** be made based on the history of typical symptoms and/or physical examination findings with typical clinical signs. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |
| **4.04** | To make the clinical presumptive diagnosis of urethritis, at least one of the following symptoms or clinical signs **should** be present:<br>- urethral discharge,<br>- dysuria or alguria,<br>- burning, itching, or pain in the area of distal urethra or external urethral meatus. | ↑↑ | Consensus-based recommendation, consensus (93%) |
| **4.06** | Especially in case dysuria is the primary complaint, cystitis (bladder inflammation) and infection of the upper urinary tract **should** be ruled out as a differential diagnosis, if one or more of the following symptoms or signs are also present:<br>- pollakiuria, nocturia, imperative urge to urinate, incontinence,<br>- macrohematuria, clouding of urine,<br>- suprapubic pain,<br>- fever, chills, systemic symptoms,<br>- history of previous cystitis,<br>- no history of sexual contacts. | ↑↑ | Consensus-based recommendation, consensus (86%)<br>Based, among others, on the information of the S3 guideline "*Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei erwachsenen Patienten*" (AWMF reg. no.: 043–044)[98] |
| **4.07** | If cystitis or infection of the upper urinary tracts is considered as a differential diagnosis, the recommendations of the S3 guidelines "*Epidemiologie, Diagnostik, Therapie, Prävention und Management unkomplizierter, bakterieller, ambulant erworbener Harnwegsinfektionen bei erwachsenen Patienten*" (AWMF reg. no.: 043–044)[98] or the S2k guideline "*Harnwegsinfektionen im Kindesalter - Diagnostik, Therapie und Prophylaxe*" (AWMF reg. no.: 166-004)[99] **should** be considered for diagnosis and therapy. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

## Clinical classification

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| **4.08** | Based on the suspected etiology, urethritis may be classified as a suspected gonococcal urethritis (GU) or non-gonococcal urethritis (NGU). Criteria for the clinical classification can be found in the Chapter "Diagnostic workup". | Consensus-based statements, strong consensus (100%) |
| **4.09** | The classification as GU or NGU primarily serves to guide the selection of an appropriate empirical antibiotic therapy. However, it does not exempt from the need to conduct further diagnostic tests to identify the pathogen(s) and any potential co-infections (see Chapter "Diagnostic workup"). | |

The initial classification as gonococcal urethritis (GU) or non-gonococcal urethritis (NGU) is an established method to select an appropriate empirical antibiotic therapy.[9,100] The classification is based on clinical and microscopic criteria (see Chapter "Diagnostic workup").[9,10,100,101] The clinical diagnosis of GU does not exclude co-infections with other pathogens. Likewise, the clinical diagnosis of NGU does not exclude infection with *N. gonorrhoeae* with certainty. Moreover, no constellation of symptoms has been identified in NGU that would be associated with a specific causative pathogen.[102] For the definite identification of the pathogen and potential co-infections, additional diagnostic tests beyond the classification as GU or NGU are, therefore, required.

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| **4.10** | Urethritis is referred to as chronic urethritis, if the subjective symptoms and/or clinical signs of urethritis persist for more than six weeks after adequate antibiotic therapy or recur without renewed pathogen detection. | Consensus-based statement, strong consensus (100%) |

No internationally established criteria for the classification of acuity of urethritis have been identified. In clinical studies, urethritis is usually referred to as chronic if the subjective symptoms and/or clinical signs persist for more than several weeks after performing adequate antibiotic

therapy or recur without renewed pathogen detection.[60,103–105] Given the more elaborate search for causes required in these cases, it is the opinion of the guideline commission that a clear distinction concerning the definition of chronic urethritis and acute urethritis is useful.

Figure 1 shows a flowchart for the syndrome-oriented management of patients with symptoms or clinical signs of penile urethritis.

## DIAGNOSTIC WORKUP

### Initial classification as gonococcal or non-gonococcal urethritis

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| **5.11** | For initial classification of acute urethritis as gonococcal urethritis (GU) or non-gonococcal urethritis (NGU), the presence of urethral discharge and its quality **should** be assessed (purulent vs. non-purulent). | ↑↑ | Evidence-based recommendation, see long version/evidence report, strong consensus (100%) |
| **5.12** | If urethral discharge is present, additional microscopic assessment of a urethral smear after methylene blue or Gram staining **may be considered** for the initial classification of acute urethritis as GU or NGU. | **0** | Evidence-based recommendation, see long version/evidence report, consensus (79%) |
| **5.13** | In acute urethritis, the clinical diagnosis of suspected GU **should** be made in case of the following constellation:<br>- purulent (yellowish-greenish) urethral discharge and not examined microscopically *or*<br>- microscopic detection of polymorphonuclear granulocytes with intraleukocytic diplococci. | ↑↑ | Evidence-based recommendation, see long version/evidence report, consensus (80%) |
| **5.14** | In acute urethritis, the clinical diagnosis of suspected NGU **should** be made in case of the following constellation:<br>- mucoid (aqueous-clear) or mucopurulent (whitish-opaque) urethral discharge and not examined microscopically *or*<br>- microscopic detection of polymorphonuclear granulocytes but no evidence of intraleukocytic diplococci *or*<br>- no apparent discharge, but other clinical signs (e.g., erythema of external urethral meatus) and/or subjective symptoms of urethritis (e.g., dysuria, alguria, itching of distal urethra). | ↑↑ | Evidence- and consensus-based recommendation, see long version/evidence report, consensus (87%) |

The first assessment for initial classification of urethritis is based on the inspection of urethral discharge. A diagnostic study investigating the diagnostic accuracy of the clinical assessment of the discharge for categorization as GU or NGU was identified.[106] The data show that the inspection of urethral discharge presents an important basis for initial classification of urethritis. To promote an antibiotic stewardship approach, the guideline group has decided to recommend a specific categorization: urethritis with purulent (yellowish-greenish) discharge should be classified as GU and urethritis with mucopurulent (whitish-opaque) or mucoid (aqueous-clear) discharge as NGU (sensitivity: 61.9% (95% CI: 48.8–73.9), GRADE ++OO; specificity: 91.5% (95% CI: 79.6–97.6), GRADE +++O; n = 154, 1 study[106]). Compared to a more sensitive categorization classifying also mucopurulent discharge as indicator for GU, this reduces the cases of urethritis with false-positive classification as GU, which would entail overtreatment on empirical administration of ceftriaxone.

Another cost-effective analysis with immediately available results is microscopic assessment of a urethral smear after methylene blue or Gram staining. Here, classification of urethritis is based on the identification of intraleukocytic diplococci, that is, on the direct microscopic detection of *N. gonorrhoeae* in the swab preparation. The diagnostic accuracy of microscopic evaluation is better than that of clinical inspection alone (sensitivity: 83.0% [95% CI: 75.1–88.7], GRADE ++OO; specificity: 98.4% [95% CI: 92.2–99.7], GRADE +++O, n = 1,742, 6 studies[45,47,107–110]). It should be noted, however, that this procedure is often unavailable in the outpatient setting while it also requires practical experience to achieve the levels of diagnostic accuracy presented here. Due to the frequent lack of availability and feasibility in clinical routine, the guideline commission has decided to provide an open recommendation for microscopy despite the diagnostic benefit.

If no discharge is apparent and there is no evidence for a specific cause in medical history, it is consensus among the guideline commission that urethritis should be classified initially as NGU.

### Microbiological standard diagnostics

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| **5.15** | In urethritis associated with urethral discharge, a meatal/urethral swab for microbiological culture and resistance testing of *N. gonorrhoeae* **should** be performed. | ↑↑ | Evidence-based recommendation, see long version/evidence report, consensus (77%) |

While nucleic acid amplification testing (NAAT) procedures enable only very limited statements about the antimicrobial susceptibility of gonococci, microbial cultivation allows for broad and phenotypic resistance testing.

Given the problematic resistance situation and the worldwide increasing numbers of cases of *extensively drug resistant N. gonorrhoeae* isolates, including resistance to

ceftriaxone, the microbiological culture-based detection of *N. gonorrhoeae*, in addition to laboratory detection using NAAT, is important for both planning of the individual treatment in case of initial therapy failure and strengthening the nationwide monitoring of antimicrobial resistance of *N. gonorrhoeae*.[111] Given that gonococci are bacteria relatively sensitive to the environment, their transport should be as short as possible and in correct transport media for microbiological culture.

## Molecular biological standard diagnostics

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| **5.16** | Irrespective of the initial classification of acute urethritis as GU or NGU, additional NAAT of a meatal/urethral swab or first void urine for *N. gonorrhoeae* and *C. trachomatis* **should** be performed. | ↑↑ | Evidence- and consensus-based recommendation, see long version/evidence report, strong consensus (100%) |
| **5.17** | In addition, NAAT of a meatal/urethral swab or first void urine for *M. genitalium* **might** be performed. | ↑ | |

Based on the expected relative frequency and in consideration of costs and benefit, the guideline commission recommends to initially perform NAAT for *N. gonorrhoeae*, *C. trachomatis*, and, if deemed appropriate, *M. genitalium* in acute urethritis. The reason for the conditional recommendation for NAAT for *M. genitalium* is the controversial discussion about *M. genitalium*, including considerations regarding the usefulness of immediate molecular diagnostic testing in individuals with acute urethritis. This is based on the widespread epidemiological distribution of *M. genitalium* infections in populations with increased probability for infection,[8,112] and their often asymptomatic and, in part, self-limiting course.[113,114] In contrast to *C. trachomatis* infections, *M. genitalium* is particularly challenging to treat due to its problematic resistance profile.[115–118]

Both meatal/urethral swabs and first void urine may be used for the molecular genetic diagnosis of *N. gonorrhoeae*, *C. trachomatis*, and *M. genitalium*. Data on diagnostic accuracy of NAAT from first void urine were identified in seven studies for *N. gonorrhoeae*[119–125], in eight studies for *C. trachomatis*[119–121,123,125–128], and in two studies for *M. genitalium*.[68,129] For all pathogens mentioned, a good (> 85%) to very good (> 95%) sensitivity and a consistently very good specificity (> 98.5%) of NAAT from first void urine compared to urethral swab was found [GRADE (+++O)–(++++)]. It should be considered that collection of urethral swabs is often experienced as painful. Diagnostic workup by means of first void urine may, therefore, be preferred. It should be noted, however, that prior to sample collection by first void urine, a period of at least two hours of urinary abstinence is required.

Examination of the diagnostic accuracy of meatal swabs compared to urethral swabs was not part of the systematic literature assessment for this guideline. There are, however, several clinical studies suggesting that the sensitivity of a meatal swab for the detection of *C. trachomatis*, *N. gonorrhoeae*, and *M. genitalium* is comparable with that of a urethral swab or first void urine.[130–132]

## Molecular diagnostic resistance tests

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| **5.18** | If contraindications to cephalosporins exist, molecular diagnostic testing of *N. gonorrhoeae* for resistance markers to ciprofloxacin **may be considered**. | **0** | Evidence-based recommendation, see long version/evidence report, consensus (93%) |

In two identified studies, the diagnostic accuracy of molecular diagnostic resistance tests of *N. gonorrhoeae* to ciprofloxacin was examined.[133,134] Compared to microbiological resistance tests, molecular diagnostic tests had a sensitivity of 98.2% (95% CI: 75.2–99.9, n = 66, GRADE ++OO) and a specificity of 93.2% (95% CI: 59.6–99.2, n = 66, GRADE ++OO). Despite these positive data, the guideline commission recommends to conduct the resistance test only in case of contraindications to cephalosporins, given that due to the profile of adverse events (AEs) and the Direct Healthcare Professional Communication (*Rote-Hand-Brief*) to fluoroquinolones,[135] ciprofloxacin should only be used if no therapeutic alternatives are available.

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| **5.19** | If NAAT for *M. genitalium* is performed, this **might** be accompanied by molecular diagnostic tests of *M. genitalium* for resistance markers to macrolides and fluoroquinolones. | ↑ | Evidence- and consensus-based recommendation, see long version/evidence report, strong consensus (100%) |

*M. genitalium* is a bacterial pathogen difficult to treat due to increasing resistance to macrolide antibiotics and fluoroquinolones.[112,136] As part of the systematic review, four studies were identified assessing molecular genetic tests for resistance markers to macrolides.[38,137–139] These demonstrated good sensitivity (80.4%, 95% CI: 66.5–89.5) and specificity (79.1%, 95% CI: 62.5–89.6%), n = 103, GRADE ++OO. No studies were identified assessing the diagnostic accuracy of resistance tests to fluoroquinolones in a sufficiently large cohort. Based on the diagnostic properties, the guideline commission suggests to perform also a molecular diagnostic resistance test to macrolides in addition to NAAT for *M. genitalium*. The conditionality of the recommendation is based on the currently still lacking nationwide availability in Germany.

# THERAPY

## Indication for empirical antibiotic therapy

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| **6.23** | The indication for empirical antibiotic therapy before pathogen detection **should** be assessed on an individual basis. The following criteria support the decision-making:<br><br>Criteria that favor an empirical antibiotic therapy:<br>- clearly objectifiable symptoms (e.g., purulent discharge),<br>- high level of distress, pronounced subjective complaints,<br>- practicability, patient not available for follow-up,<br>- high risk of further transmission,<br>- clear temporal association with sexual exposure,<br>- co-treatment in the sense of partner therapy according to pathogen-specific guidelines.<br><br>Criteria that disfavor an empirical antibiotic therapy:<br>- absence of objectifiable symptoms,<br>- long-lasting symptoms,<br>- low level of distress, minimal subjective complaints,<br>- recent antibiotic treatment(s) of the same symptom complex. | ↑↑ | Consensus-based recommendations, strong consensus (100%) |
| **6.24** | In chronic urethritis, an empiric antibiotic treatment **should not** be performed. | ↓↓ | |

Given increasing levels of antimicrobial resistance, the question is frequently raised whether empirical antibiotic therapy of urethritis prior to pathogen detection is useful.[140] Currently, however, international guidelines and reviews on penile urethritis generally recommend an immediate empirical antibiotic therapy based on the differentiation of GU and NGU.[100,141–145]

The rationale for performing empirical antibiotic therapy is *(1)* the expected rapid amelioration of symptoms in case of adequate antibiotic treatment, *(2)* the reduction of complications of persistent urethral infections, and *(3)* a reduction of further transmission of the infection.

Numerous data are available on the reduction of symptom load by adequate antibiotic therapy. To the knowledge of the guideline commission, however, there are no reliable data substantiating the benefit of immediate therapy with respect to reduction of complication rates and continued transmission with empirical data. From the perspective of the guideline commission, however, both aspects present plausible arguments supporting the potential benefit of empirical antibiotic therapy in addition to symptom reduction. Given the unclear data concerning this aspect, the guideline commission has decided to recommend decision-making on an individual basis with the aid of decision criteria.

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| **6.25** | If no empiric antibiotic therapy was performed at the time of the initial presentation, the antibiotic treatment **should** be initiated as early as possible after pathogen detection according to the pathogen-specific therapies recommended below. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |
| **6.26** | If an empiric antibiotic therapy was administered at the time of the initial presentation, it **should** be assessed after pathogen detection whether the treatment has covered all identified pathogens considered as relevant according to the pathogen-specific therapies recommended below. A potentially required additional treatment **should** be initiated as soon as possible. | ↑↑ | |

## Empirical therapy for suspected gonococcal urethritis

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| **6.27** | In case of clinically suspected gonococcal urethritis (GU) and indication for empirical therapy, treatment with ceftriaxone 1,000–2,000 mg i.v. or i.m. single dose **should** be performed.[1] | ↑↑ | Evidence- and consensus-based recommendation, see long version/evidence report, strong consensus (100%) |
| **6.28** | Due to the relevant risk of co-infection in GU, additional treatment with doxycycline 100 mg p.o. twice daily for 7 days **might** be performed.[2] | ↑ | Evidence-based recommendation, see long version/evidence report, consensus (81%) |
| **6.29** | The additional treatment with doxycycline **might be omitted** if treatment of a potential co-infection is assured in the context of a timely follow-up. | ↓ | Consensus-based recommendation, consensus (81%) |
| **6.30** | In case of GU and contraindications to doxycycline, a combined empirical treatment with ceftriaxone as mentioned above and azithromycin p.o. according to the 4-day treatment regimen (day 1: 1,000 mg, days 2–4: 500 mg p.o.) **may be considered** as an alternative, if follow-up is not assured.[3] | **0** | Evidence-based recommendation, see long version/evidence report, consensus (93%) |

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| **6.31** | If the use of the combined empirical treatment of GU mentioned above or the mentioned alternative is not possible due to contraindications, treatment of uncomplicated urethritis **should** only be initiated after pathogen detection. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

[1]This dosage represents an off-label use. The use of ceftriaxone at a dose > 1,000 mg has not been studied in controlled trials on treatment of urethritis, but has been evaluated for other indications. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[2]This dosage information represents an off-label dose for individuals with a body weight below 70 kg. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[3]The dosage according to the 4-day treatment regimen represents an off-label use. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.

The detailed rationale for the recommendation concerning the use of ceftriaxone in case of clinically suspected GU with indication for empirical antibiotic therapy can be found in other chapters of this guideline ("Initial classification as gonococcal or non-gonococcal urethritis", "Antibiotic therapy if *N. gonorrhoeae* is detected"). In addition, the following aspects must be considered: In case of a urethral infection with *N. gonorrhoeae*, there is a high probability for the presence of urethral co-infections with other bacterial pathogens, such as *C. trachomatis* (approximately 21%) and *M. genitalium* (approximately 11%), see "Etiology and pathogen epidemiology". Especially due to the high risk of urethral co-infection with *C. trachomatis*, the guideline commission recommends to cover this pathogen in the context of an empirical antibiotic therapy, unless timely follow-up for the treatment of a potential co-infection is assured. The rationale for the recommendation of doxycycline or alternatively azithromycin according to the 4-day treatment regimen for the treatment of potential co-infections with *C. trachomatis* and/or *M. genitalium* can be found in the sections "Antibiotic therapy if *C. trachomatis* is detected" and "Antibiotic therapy if *M. genitalium* is detected".

## Empirical therapy for suspected non-gonococcal urethritis

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| **6.32** | In case of clinically suspected non-gonococcal urethritis (NGU) and indication for empirical therapy, treatment with doxycycline 100 mg p.o. twice daily for 7 days **should** be performed.[1] | ↑↑ | Evidence- and consensus-based recommendation, see long version/evidence report, strong consensus (100%) |
| **6.33** | In case of NGU and contraindications to doxycycline, an empirical treatment with azithromycin p.o. according to the 4-day treatment regimen (day 1: 1,000 mg, days 2–4: 500 mg p.o.) **might** be performed as an alternative, if follow-up is not assured.[2] | ↑ | |

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| **6.34** | If the use of the empirical treatment mentioned above or the mentioned alternative is not possible due to contraindications, treatment of uncomplicated urethritis **should** only be initiated after pathogen detection. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

[1]This dosage information represents an off-label dose for individuals with a body weight below 70 kg. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[2]The dosage according to the 4-day treatment regimen represents an off-label use. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.

In NGU, infections with *C. trachomatis* (26% [95% CI: 21%–31%], n = 4,779, 16 studies,[58,60–62,65,67,73,146–154] GRADE [++OO]) and *M. genitalium* (17% [95% CI: 11%–26%], n = 4,596, 12 studies,[58,60–62,65,67,146,147,149,154–156] GRADE [+OOO]) are identified most often. While *U. urealyticum* (20% [95% CI: 11%–33%], n = 847, 6 studies,[58,65,73,147,150,152] GRADE [+OOO]) is also often detected, the clinical relevance for the detection of *U. urealyticum* must be assessed on an individual basis.

Doxycycline is considered the treatment of choice for the treatment of both *C. trachomatis* and *U. urealyticum* (see respective sections of the guideline). With respect to the treatment of *M. genitalium*, insufficient efficacy of doxycycline must be anticipated. However, to limit the use of azithromycin, which is increasingly problematic with respect to resistance in *N. gonorrhoeae* and *M. genitalium*, as much as possible, the guideline commission still favors the use of doxycycline as empirical first-line therapy in NGU. In case of contraindication or other reasons against the use of doxycycline, and if empirical therapy with azithromycin is performed, the 4-day treatment regimen should be considered with respect to dosage and dosage regimen as this may promote azithromycin resistance in *M. genitalium* to a lesser degree (see section "Antibiotic therapy if *M. genitalium* is detected").

In several studies identified as part of the systematic literature review, participants were treated and assessed irrespective of the identified pathogen after clinical classification as NGU.[87,157] In a meta-analysis, no statistically significant difference was calculated for "clinical cure" when azithromycin 1,000 mg p.o. as single dose was compared with doxycycline 100 mg p.o. twice daily for 7 days (RR 1.02 [95% CI: 0.95–1.10], n = 673, 2 randomized controlled trials [RCTs],[87,157] GRADE +++O). With respect to AEs, one of the studies[87] showed also no significant difference (RR 1.03 [95% CI 0.69–1.54], n = 422, GRADE ++OO).

## Antibiotic therapy if *N. gonorrhoeae* is detected

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| **6.35** | If *N. gonorrhoeae* is detected, treatment with ceftriaxone 1,000–2,000 mg i.v. or i.m. single dose **should** be performed as therapy of first choice.[1] | ↑↑ | Evidence- and consensus-based recommendations, see long version/evidence report, strong consensus (100%) |
| **6.36** | In case of contraindications to cephalosporins and detection of *N. gonorrhoeae* with sensitivity to azithromycin confirmed by culture, treatment with azithromycin p.o. **might** be performed;<br>- if co-infection with *M. genitalium* was excluded, single dose at a dosage of 1,000 mg,<br>- if co-infection with *M. genitalium* was not excluded, according to the 4-day treatment regimen (day 1: 1,000 mg, days 2–4: 500 mg each).[2] | ↑ | |
| **6.37** | In case of contraindications to cephalosporins and detection of *N. gonorrhoeae* with sensitivity to ciprofloxacin confirmed by molecular diagnosis or culture, treatment with ciprofloxacin 500 mg p.o. single dose **may be considered**.[3] | **0** | |
| **6.38** | In case of contraindications to the mentioned treatment options or therapy failure, experts in the field of sexually transmitted infections (STIs) and/or the Reference Laboratory for Gonococci at the Robert Koch Institute **should** be contacted for treatment advice. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

[1]This dosage represents an off-label use. The use of ceftriaxone at a dose > 1,000 mg has not been examined in controlled trials for the treatment of urethritis, but has been evaluated for other indications. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[2]The dosage according to the 4-day treatment regimen represents an off-label use. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[3]For the prescription of ciprofloxacin, the information of the Direct Healthcare Professional Communication (*Rote-Hand-Brief*) to fluoroquinolones has to be considered.[135] For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.

*N. gonorrhoeae* is a genetically highly variable bacterium that has acquired resistance to all classes of antibiotics. For urethral infection with *N. gonorrhoeae*, national and international guidelines recommend ceftriaxone as treatment of first choice and sometimes also ciprofloxacin if susceptibility is confirmed. Cefixime, azithromycin, and sometimes also gentamicin are recommended as therapeutic alternatives.[141,143,158]

Apart from the efficacy in clinical trials, the regional resistance situation is crucial for assessing the effectiveness of antimicrobial therapies. As of May 2023, the resistance surveillance of *N. gonorrhoeae* in Germany provided the following results:[111]

- *Ceftriaxone*: stable very low resistance level with < 1% resistant isolates,
- *Cefixime*: stable low resistance level with 1–2% resistant isolates,
- *Azithromycin*: alarming increase of isolates with reduced susceptibility (minimum inhibitory concentration > 1 mg/l) to 25.3% in 2022,
- *Penicillin*: stable high percentage of resistant isolates with 10–20% (high-level resistance), approximately 80% resistant isolates overall,
- *Ciprofloxacin*: stable very high percentage of resistant isolates with > 60%,
- *Tetracycline*: stable very high percentage of resistant isolates with > 80%, 91.2% in 2022.

In a large part of the randomized trials identified in the systematic literature review, ceftriaxone was used as reference standard for the treatment of urethral *N. gonorrhoeae* infection. For this purpose, it was studied as single dose in monotherapy or combination therapy at a dosage of 250–1,000 mg i.m. or i.v. Comparator interventions included cefixime,[159] ciprofloxacin,[160] delafloxacin,[161] ertapenem,[162] fosfomycin,[162] gentamicin,[162–164] solithromycin,[165] spectinomycin,[160] and zoliflodacin.[166] In many direct comparison studies, ceftriaxone was significantly superior to the respective comparator intervention and in none of the studies was it inferior. Apart from ceftriaxone, other antimicrobial substances have also been selected as comparator interventions in randomized trials. Some of these are currently not available because of their approval status. The most important data justifying the recommendations are presented below (for a detailed presentation of study data, see long version or evidence report).

In a non-blinded RCT,[159] the use of ceftriaxone 1,000 mg i.v. was compared with cefixime 800 mg p.o., each in combination with doxycycline. In both treatment groups, cure of urethral *N. gonorrhoeae* infection based on laboratory diagnosis was achieved in 100% of the cases (RR 1 [95% CI: 0.95–1.05], n = 77, GRADE +++O).

In another RCT, combination treatment consisting of ceftriaxone 1,000 mg i.m. plus azithromycin 2,000 mg p.o., each as single dose, was compared with combination treatment consisting of single-dose cefixime 800 mg p.o. plus doxycycline 100 mg p.o. twice daily for 7 days in case of urogenital, rectal or pharyngeal detection of *N. gonorrhoeae*.[167] In this study the efficacy of ceftriaxone/azithromycin was significantly better. The analysis stratified by anatomical localization showed cure of all urogenital and rectal *N. gonorrhoeae* infections irrespective of treatment. For pharyngeal infections, cure of all cases was also shown on treatment with ceftriaxone/azithromycin (21 of 21 patients, 100% [95% CI: 84%–100%]), but only in 50% on cefixime/doxycycline (12 of 24 patients, 50% [95% CI: 29–71%]).[167] All cases of treat-

ment failure on cefixime occurred, therefore, in pharyngeal localization, whereas no differences in efficacy between both treatment regimens were observed for genital or rectal localization.[167] A recently published meta-analysis on the efficacy of cefixime in *N. gonorrhoeae* infection of various anatomical localizations also demonstrated high efficacy in urogenital and rectal localizations (98%–100%), but a lower efficacy in a pharyngeal localization (91% on cefixime 400 mg, 82% on cefixime 800 mg).[168] Given the risk of pharyngeal co-infections in case of urethral detection of *N. gonorrhoeae* (see section "Etiology and pathogen epidemiology"), no recommendation for cefixime is given.

Although a dose of 2,000 mg ceftriaxone has not been studied in controlled trials on treatment of gonorrhea, the guideline commission argues for a dose range of up to 2,000 mg ceftriaxone (single dose) based on expert opinion. This recommendation is based on the increasing cases of *N. gonorrhoeae* isolates with enhanced minimum inhibitory concentration to ceftriaxone observed worldwide that responded only to treatment with 1,000 mg ceftriaxone[169–172] or not even to this dose.[173] The German pathogen-specific S2k guideline "*Diagnostik und Therapie der Gonorrhoe*" consented in 2019 includes also the recommendation for the use of 1,000–2,000 mg ceftriaxone i.v. or i.m. as therapy of first choice.[158]

Given that it is an antibiotic with long half-life, there are no relevant pharmacodynamic or pharmacokinetic differences between intravenous or intramuscular parenteral administration of ceftriaxone. However, it should be considered that i.m. administration is usually more painful and contraindicated in certain conditions (for example, anticoagulation, hemophilia). Short i.v. infusion is, therefore, usually the administration mode of choice.

The guideline commission argues against the use of monotherapy with azithromycin unless there are contraindications to the administration of cephalosporins and susceptibility of the respective isolate has been confirmed. Background is the increase of resistance of *N. gonorrhoeae* to azithromycin observed in recent years to currently more than 25% of the examined isolates in Germany.[111] If monotherapy with azithromycin is performed under the conditions mentioned, it should be considered whether co-infection with *M. genitalium* was excluded or not in order to prevent promotion of azithromycin resistance in *M. genitalium* in case of potential co-infection (see section "Antibiotic therapy if *M. genitalium* is detected").

Concerning ciprofloxacin, the high percentage of *N. gonorrhoeae* isolates with resistance to ciprofloxacin that is to be expected in Germany and the Direct Healthcare Professional Communication (*Rote-Hand-Brief*) to fluoroquinolones[135] restricting the use to persons without alternative therapeutic options due to rare but severe AEs must be considered. Given the restriction for the use of fluoroquinolones, the guideline commission can only make an open recommendation for ciprofloxacin even in case of an *N. gonorrhoeae* isolate with confirmed susceptibility.

In case of contraindications to the recommended treatment options or therapy failure on these treatments, other substances with antimicrobial effect may also be used. Given that in such cases the selection of a substance is often made individually and based on experience, the guideline commission recommends the consultation of experts in the field of sexually transmitted infections, for example, from the Reference Laboratory for Gonococci at the Robert Koch Institute.

## Antibiotic therapy if *C. trachomatis* is detected

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| **6.39** | If *C. trachomatis* is detected, treatment with doxycycline 100 mg p.o. twice daily for 7 days **should** be performed as therapy of first choice.[1] | ↑↑ | Evidence- and consensus-based recommendation, see long version/evidence report, strong consensus (100%) |
| **6.40** | In case of detection of *C. trachomatis* and contraindications to doxycycline, treatment with azithromycin p.o. **should** be performed;<br>- if co-infection with *M. genitalium* was excluded, at a dosage of 1,000 mg single dose,<br>- if co-infection with *M. genitalium* was not excluded, according to the 4-day treatment regimen (day 1: 1,000 mg, days 2–4: 500 mg each).[2] | ↑↑ | |
| **6.41** | In case of contraindications to the treatment options mentioned above or therapy failure, experts in the field of STIs **should** be contacted for treatment advice. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

[1]This dosage information represents an off-label dose for individuals with a body weight below 70 kg. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[2]The dosage according to the 4-day treatment regimen represents an off-label use. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.

In national and international guidelines, doxycycline or azithromycin are recommended for the treatment of urethral infections with *C. trachomatis*.[141,145,174]

During the systematic assessment of the evidence, multiple RCTs were included comparing the efficacy and safety of these two antibiotics.[87,157,175–181] The meta-analysis of the results of these trials did not provide any significant differences between doxycycline and azithromycin with respect to efficacy endpoints and safety endpoints, GRADE (+OOO)–(+++O). Cure of *C. trachomatis* based on laboratory diagnosis can be expected in 96.1% of cases on treatment with doxycycline and in 88.4% of cases on treatment with azithromycin.

*Neisseria gonorrhoeae* and *M. genitalium* represent epidemiologically relevant co-infections in urethritis associated with *C. trachomatis*: The prevalence of co-infections with *N. gonorrhoeae* is approximately 11% (95% CI: 6%–17%, n = 3,574, 18 studies,[18,27,32,33,36,38–40,43,77,79,80,82,83,182–185] GRADE +OOO), and that of co-infections with *M. genitalium* approximately 10% (95% CI: 7%–15%, n = 1,663, 17 studies,[18,26,32,33,36,38,42,43,61,65,79,80,83,146,149,154,186] GRADE ++OO). Based on the comparable efficacy and safety and the problematic resistance of both pathogens to azithromycin, it is the opinion of the guideline commission that doxycycline should be generally preferred to avoid azithromycin as much as possible.

In case of contraindications or other reasons against doxycycline, azithromycin is, however, the treatment of choice for infections with *C. trachomatis*. With respect to the dosage regimen of azithromycin it should be considered, according to the guideline commission, whether co-infection with *M. genitalium* was excluded by laboratory diagnosis or not in order to prevent promotion of azithromycin resistance in *M. genitalium*; see section "Antibiotic therapy if *M. genitalium* is detected".

In case of contraindications to both doxycycline and azithromycin or therapy failure on these treatments, other antimicrobial substances may also be used for the treatment of urogenital infections with *C. trachomatis*. Given that in such cases the selection of a substance is often made individually and based on experience, the guideline commission recommends the consultation of experts in the field of STIs.

The specified treatment recommendations apply for *C. trachomatis* of serovars D–K. According to the data obtained from the epidemiological reviews for this guideline, the proportion of urethral infections with serovars L1–L3 as cause of urethritis should be very low (see section "Etiology and pathogen epidemiology"). If serovars L1–L3 are detected by molecular diagnosis, longer treatment duration is required.

## Antibiotic therapy if *M. genitalium* is detected

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| **6.42** | If *M. genitalium* is detected without molecular diagnostic resistance testing or without detection of macrolide resistance-associated mutations (MRAMs), treatment with azithromycin according to the 4-day treatment regimen (day 1: 1,000 mg, days 2–4: 500 mg each) **might** be performed as therapy of first choice.[1] | ↑ | Evidence- and consensus-based recommendation, see long version/evidence report, consensus (87%) |
| **6.43** | If *M. genitalium* is detected, treatment with moxifloxacin 400 mg p.o. once daily for 7 days **might** be performed,[2] if:<br>- contraindications to treatment with azithromycin exist *or*<br>- MRAMs have been detected in molecular genetic tests *or*<br>- the transmission setting suggests a high probability for resistance to azithromycin *or*<br>- there was no response to the treatment with azithromycin mentioned above. | ↑ | Evidence- and consensus-based recommendations, see long version/evidence report, strong consensus (100%) |
| **6.44** | In case of no response or contraindications to the administration of azithromycin and moxifloxacin, treatment with sitafloxacin 100 mg p.o. twice daily for 7 days **may be considered**, if *M. genitalium* is detected (currently not available in Germany).[3] | **0** | Evidence- and consensus-based recommendations, see long version/evidence report, strong consensus (100%) |
| **6.45** | In case of contraindications to the treatment options mentioned above or therapy failure, experts in the field of STIs **should** be contacted for treatment advice. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

[1] The dosage according to the 4-day treatment regimen represents an off-label use. For the treatment of individuals younger than 18, it should be assessed on an individual basis whether dose adjustment is required.
[2] This indication represents an off-label use. For the prescription of moxifloxacin, the information of the Direct Healthcare Professional Communication (*Rote-Hand-Brief*) to fluoroquinolones has to be considered.[135] Moxifloxacin is not approved for the treatment of individuals younger than 18.
[3] Currently (mid-2024), sitafloxacin is not approved in Germany/Europe.

*M. genitalium* is a controversially discussed pathogen. Although the association of urethral *M. genitalium* infection with urethritis has been established in multiple epidemiological studies,[32,56–69] and *M. genitalium* also represents a relevant pathogen with respect to pathogen epidemiology of urethritis, there is disagreement concerning the indication of screening of asymptomatic individuals, initial molecular diagnostic tests for *M. genitalium* in individuals with symptoms of urethritis, and the requirement for treatment of asymptomatic *M. genitalium* infections (see section "Molecular biological standard diagnosis").

In recent international guidelines, a "resistance-guided antimicrobial therapy" with sequential administration of doxycycline and azithromycin or moxifloxacin is recommended.[141,187,188] For this purpose, initial treatment with doxycycline followed by treatment with either azithromycin or moxifloxacin, depending on implementation and results of molecular diagnostic resistance tests, is usually recommended.[141,187,188] Despite a low level of evidence, an extended dosage regimen of 3,[188] 4,[141,187] or 5[145] days is mostly recommended for azithromycin.[141,142,187]

Monotherapy of *M. genitalium* with doxycycline results in relatively low cure rates of approximately 30% or less (cure based on laboratory diagnosis) that are, moreover, statistically significantly lower than for monotherapy with single-dose azithromycin 1,000 mg p.o. (RR 1.81 [95% CI: 1.14–2.87], n = 149, 2 RCTs,[87,157] GRADE ++OO). Therefore, the guideline commission has decided to give no recommendation for doxycycline. Interestingly, the other therapeutic options described here are mostly used in the context of sequential combination therapy after administration of doxycycline. On the one hand, this has pragmatic reasons as doxycycline is the recommended empirical therapy of choice in NGU and is, therefore, used anyway in many cases before pathogen detection of *M. genitalium*. On the other hand, data are available suggesting that pretreatment with doxycycline results in reduction of the pathogen load and may thus promote the response to the antimicrobial combination therapy.[41,189]

Cure rates on azithromycin are largely dependent on the susceptibility of the respective *M. genitalium* isolate. Therefore, the absolute numbers concerning cure on azithromycin treatment based on laboratory diagnosis from the identified studies should be interpreted with caution.

Data on the resistance situation of *M. genitalium* in Germany are limited; in a study on MSM positive for *M. genitalium*, macrolide resistance-associated mutations (MRAMs) and fluoroquinolone resistance-associated mutations (QRAMs) were found in 79.9% and 13.0%, respectively.[136] Similar results have been obtained in a systematic review.[112] According to the opinion of the guideline commission, however, these data cannot be transferred to the general population. The proportion of *M. genitalium* infections with MRAMs is probably significantly lower in the heterosexual population. In Germany, molecular diagnostic resistance tests are currently not available in all medical settings (see section "Molecular diagnostic resistance tests").

No studies directly comparing different dosage regimens for azithromycin have been identified. A meta-analysis combining case series and mostly retrospective, non-comparative observational studies, obtained evidence that a single dose of azithromycin 1,000 mg p.o. in *M. genitalium* may be less effective and cause more resistances than a 5-day treatment regimen.[190] This meta-analysis was not included in the systematic assessment of the evidence, given that the meta-analysis itself and the data combined therein have important methodological limitations restricting the confidence in the conclusions. Moreover, the evidence included in the meta-analysis is heterogeneous with respect to its results and individual studies also concluded that no differences exist between azithromycin for 5 days and single-dose administration.[138,191]

In recent non-comparative cohort studies from Australia, efficacy was shown for sequential therapy with azithromycin (first, doxycycline 100 mg p.o. twice daily for 7 days, then azithromycin p.o. day 1: 1,000 mg, days 2–4: 500 mg) in 95% of *M. genitalium* infections without MRAM detection.[192,193] Based on the available evidence and in the opinion of the guideline commission, azithromycin should be given according to the mentioned 4-day treatment regimen to reduce the risk of promoting macrolide resistance despite the relatively low evidence for this approach.

Constellations where the use of moxifloxacin is an alternative are presented in recommendation 6.43. Two uncontrolled cohort studies reported cure of urogenital *M. genitalium* infections in 91% and 85% of the cases, respectively, on sequential therapy first with doxycycline followed by moxifloxacin.[192,193] In another uncontrolled study, cure based on laboratory diagnosis was achieved after therapy with moxifloxacin in 53 of 60 cases (88.3%) that had not been cured by initial treatment with azithromycin.[194] In the mentioned studies, AEs were reported in 30% and 44% of the cases, respectively. Four of 214 patients reported severe gastrointestinal symptoms or severe dizziness.[192,193]

Sitafloxacin may present an alternative for the treatment with moxifloxacin.[195] On sequential therapy with doxycycline and sitafloxacin, cure was observed in more than 90% of the cases and thus a similar efficacy with a lower rate of AEs compared to sequential therapy with moxifloxacin (RR 0.52, [95% CI: 0.37–0.73], n = 571, three separate cohort studies,[192,193,195] GRADE +OOO). Given that only uncontrolled studies were identified and sitafloxacin is currently not approved in Germany (as of mid-2024), the guideline commission gives only an open recommendation. If necessary, sitafloxacin must be ordered via the international pharmacy and respective information must be provided to the patient.

According to the Direct Healthcare Professional Communication (*Rote-Hand-Brief*) dispatched by the German Federal Institute for Drugs and Medical Devices, fluoroquinolones should be used with caution due to the risk of severe AEs impairing the quality of life.[135] Moreover, moxifloxacin is not approved for individuals younger than 18 years in Germany.

Another antimicrobial substance tested for the treatment of *M. genitalium* is pristinamycin. In a cohort study investigating various dosages, the best cure rates were observed on treatment with pristinamycin 1,000 mg three and four times daily with 74% and 75% of the studied cases, respectively.[196] Given that pristinamycin is not sold in Germany, it must be ordered via the international pharmacy. Based on the current status (mid-2024), however, pristinamycin is not even available via the international pharmacy. Therefore, the guideline commission has decided to provide no recommendation for pristinamycin.

In addition to the evidence summarized here, case series and case descriptions on other antimicrobial substances are available, for example, on josamycin and minocycline.[41,197] In the opinion of the guideline commission, however, not enough data are available for these substances to provide specific recommendations. In case of contraindications to azithromycin, moxifloxacin, and sitafloxacin or therapy

failure on these treatments, the guideline commission recommends consultation of experts in the field of STIs for the treatment of urogenital *Mycoplasma genitalium* infections.

## COUNSELLING AND FOLLOW-UP

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| **6.53** | Individuals with a clinical diagnosis of acute urethritis **should** be informed to maintain sexual abstinence for at least 1 week after completing antibiotic treatment or longer if symptoms persist. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |
| **6.54** | Individuals with clinical diagnosis of acute urethritis **should** be informed that sexual partners of the last weeks before onset of symptoms should be notified about the diagnosis and the need of respective diagnostic workup and, if appropriate, therapy. | ↑↑ | Consensus-based recommendation, strong consensus (100%) |

The above-mentioned recommendations of sexual abstinence and notification of partners were given in order to interrupt transfection chains and prevent reinfections.[198,199]

In German pathogen-specific guidelines, it is recommended to involve the sexual partners of the last six months in case of diagnosis of chlamydia infections and diagnosis of asymptomatic gonorrhea.[158,174] In the view of the guideline commission this may be realistic in some settings. In other settings it may be more useful to limit the time period of the sexual partners to be notified to the most likely time of infection in order to keep the notification of partners within realistic and useful limits. Overall, there is insufficient scientific evidence concerning the incubation times of the most common pathogens of urethritis. While periods of a few days to several weeks, sometimes even several months, are typically reported in publications, this is not supported by scientific evidence.

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| **6.55** | Upon diagnosis of urethritis, testing for HIV and other STIs **should** be offered in addition to the diagnostic workup for urethritis recommended in this guideline. Examples for rational and risk-adapted tests are given in Table 3 below. | ↑↑ | Evidence- and consensus-based recommendation, see long version/evidence report, strong consensus (100%) |

Every medical contact with a diagnosis of an STI offers the opportunity to conduct meaningful prevention work, including secondary and tertiary prevention. Undetected HIV or syphilis infections may be detected allowing for their appropriate treatment.

In general, the diagnosis of an STI should be regarded as indicator condition for an unknown HIV infection.[200,201] Accordingly, both the World Health Organization and the European guideline on HIV testing recommend to offer an HIV test upon diagnosis of STI.[202,203] A substantial proportion of approximately one third of the HIV infections in Germany are only detected with advanced immune defect.[204] This is associated with increased morbidity and poorer prognosis[205–207] and with the risk of continued transmission that can be prevented by antiretroviral therapy.[208,209] Accordingly, not offering an HIV test in case of symptoms or diagnosis of an STI is regarded as "missed opportunity".[210]

Based on the data on prevalence of urethral and other co-infections and analogous to the recommendations of the pathogen-specific guidelines on the management of gonorrhea and chlamydia infection,[158,174] the guideline commission gives a strong recommendation for tests for HIV infection and other STIs. The spectrum of STIs that should be considered for risk-adapted testing includes the following infections: HIV, syphilis, hepatitis B and C, as well as infections with *C. trachomatis*, *N. gonorrhoeae*, and, if appropriate, *M. genitalium* of the rectum and pharynx. Examples for risk-adapted and rational testing are shown in Table 3.

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|---|---|---|---|
| **6.56** | Individuals with clinical diagnosis of acute urethritis **should** be informed about measures to reduce the risk of HIV and other STIs. This includes in particular:<br>- protective effect of condoms (depending on the infectious disease, reduction of risk by approximately 50% to 90%)<br>- depending on the risk, HIV pre-exposure prophylaxis (> 95% reduction of risk of HIV infection in case of therapy adherence)<br>- vaccination against vaccine-preventable STIs | ↑↑ | Consensus-based recommendation, strong consensus (100%) [6 abstentions from voting due to conflicts of interest] |

The risk of recurrent infection is significantly increased after the initial diagnosis of STI.[211–213] According to the opinion of the guideline commission, individuals with clinical diagnosis of urethritis should, therefore, be informed about measures for prevention of HIV infections and other STIs.

This includes information about the protective effect of condoms (reduction of HIV risk by approximately 70% to 90%;[214–216] heterogeneous data for other STIs, especially for *C. trachomatis* and *N. gonorrhoeae*, data indicate a limited protection[217]), HIV pre-exposure prophylaxis (PrEP) as an established and effective measure for the prevention of HIV infections,[218] vaccinations against vaccine-preventable STIs (for example, HPV,[219,220] hepatitis A/B, meningococci, mpox).[219] Depending on settings and practices, it is sometimes useful to refer to the possibility of doxycycline post-exposure prophylaxis (doxy PEP).[221]

**TABLE 3** Examples of risk-adapted testing for other sexually transmitted infections.

| Situation and corresponding rational and risk-adapted testing | |
|---|---|
| ***Individuals not in regular medical consultation with competence in the field of HIV and STIs…*** | |
| Offer of immediate testing:<br>- HIV serology (combined antigen/antibody test of 4th generation)<br>- Syphilis serology<br>- Hepatitis B and C serology<br>- Rectal and pharyngeal pathogen swabs for *C. trachomatis*, *N. gonorrhoeae*, *M. genitalium*, if appropriate<br>Offer of another test after the end of the diagnostic window (or reference to other tests):<br>- HIV serology (combined antigen/antibody test of 4th generation)<br>- Syphilis serology | |
| ***Individuals in regular medical consultation with competence in the field of HIV and STIs every three months…*** | |
| … because they use *HIV pre-exposure prophylaxis (PrEP)* | Reference to HIV and syphilis tests and pathogen swabs at the next scheduled outpatient specialist follow-up visit (PrEP check) within the next 3 months. |
| … because they *live with HIV* | Reference to syphilis tests and pathogen swabs at the next scheduled outpatient specialist follow-up visit (e.g. routine HIV examination) within the next 3 months. |

Erläuterungen: Zustimmung zu dieser Tabelle: 93%.
Explanations: Agreement with this table: 93%.

| | | | |
|---|---|---|---|
| **6.57** | Individuals with a clinical diagnosis of acute urethritis **should** be informed that a follow-up visit should be scheduled, if the symptoms persist for more than two weeks after completion of the antibiotic therapy or in case of recurrent symptoms. | ↑↑ | Consensus-based recommendations, strong consensus (100%) |
| **6.58** | In case of initial detection of *N. gonorrhoeae*, *C. trachomatis*, or *M. genitalium*, a follow-up for test of cure **might** be scheduled 6 to 12 weeks after completion of the antibiotic therapy. | ↑ | |

Generally, cessation of symptoms can be expected within one to two weeks after the diagnosis of urethritis.[78,222] If symptoms and clinical signs of urethritis persist for more than 2 weeks after completion of therapy, a follow-up visit should be scheduled to exclude therapy failure, reinfection, or insufficiently treated co-infection. Moreover, in the opinion of the guideline commission, a follow-up might be scheduled within a time window of 6 to 12 weeks.

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## CONFLICT OF INTEREST STATEMENT

A complete list of the declared conflicts of interests is available in the guideline report at https://www.awmf.org/leitlinien/detail/ll/013-099.html.

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