GUIDELINE

2009 European Guideline on the Management of Male Non-gonococcal Urethritis

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INTRODUCTION

Urethritis, or inflammation of the urethra, in men is characterized by discharge and/or urethral symptoms such as dysuria or urethral itching, but may be asymptomatic. Urethritis is mainly due to sexually transmitted pathogens. The diagnosis of urethritis is confirmed by demonstrating an excess number of polymorphonuclear leukocytes (PMNLs) in the anterior urethra. This is usually assessed using a urethral smear, but a first-pass urine (FPU) specimen can also be used. Urethritis is described as either gonococcal, when Neisseria gonorrhoeae is detected, or non-gonococcal urethritis (NGU), when it is not. Mucopurulent cervicitis is the female equivalent of male NGU with approximately 40% of cases being due to infection with Chlamydia trachomatis, although female NGU due to C. trachomatis and Mycoplasma genitalium has been reported.

There are a number of uncertainties with NGU. There is significant inter-observer and intra-observer error in performing and reading urethral slides and counting PMNLs, especially in samples with low-grade inflammation. In many men with urethritis, a known pathogen is not isolated. The isolation rate varies enormously in different social settings and different European countries. The isolation rate varies enormously in different social settings and different European countries. The prevalence of the common organisms associated with NGU in more recent studies are listed in Tables 1 and 2. Reported isolation rates of pathogens is lower in more recent studies despite the use of more sensitive tests. The commonest organisms implicated are C. trachomatis and M. genitalium with the latter perhaps causing more symptoms. The exact role of ureaplasmas in NGU has been controversial, due to conflicting observations in clinical studies. Ureaplasmas are ubiquitous microorganisms which can be isolated from 30% to 40% of healthy sexually active young men. They have recently been divided into two species: U. parvum (biovar 1) and U. urealyticum (biovar 2) and in some studies U. urealyticum has been associated to 5–10% of cases of acute NGU.

AETIOLOGY

- N. gonorrhoeae. The isolation rate varies enormously in different social settings and different European countries. N. gonorrhoeae is more common in inner city urban, deprived areas compared with more affluent neighbourhoods. The prevalence of the common organisms associated with NGU in more recent studies are listed in Tables 1 and 2. Reported isolation rates of pathogens is lower in more recent studies despite the use of more sensitive tests. The commonest organisms implicated are C. trachomatis and M. genitalium with the latter perhaps causing more symptoms.
- Chlamydia is more likely to be isolated in younger patients than M. genitalium and the two organisms rarely coexist in the same individual.
- In 30–80% of the cases with NGU neither C. trachomatis nor M. genitalium is detected.
- The isolation of Trichomonas vaginalis is dependent on the prevalence of the organism in the community, being more common in non-white ethnic groups and Eastern Europe, and greatly increases with the use of more sensitive polymerase chain reaction assays.
- T. vaginalis isolation is greater in men >30 years.
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Table 1 Prevalence of the most common pathogens detected from patients with NGU

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>C. trachomatis</td>
<td>11–43%</td>
<td>7,8,11,12,16,19,23–25,27,82</td>
</tr>
<tr>
<td>M. genitalium</td>
<td>9–25%</td>
<td>5–7,12,13,16,22,23,25,27,38,83,84</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>2–4%</td>
<td>27,32</td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>1–20%</td>
<td>28,82,85–87</td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td>2–3%</td>
<td>27,33</td>
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</tbody>
</table>

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Keith Radcliffe (Editor-in-Chief), Marita van de Laar, Michel Janier, Jorgen Skov Jensen, Martino Neumann, Raj Patel, Jonathan Ross, Willem, van der Meijden, Pieter van Voorst Vader and Harald Moi
• A urinary tract infection may account for 6.4% (95% confidence interval 1.5–11.3%) of cases of NGU, although there is only one study evaluating this.\textsuperscript{31}
• Adenovirus infection may account for perhaps 2–4% of cases of symptomatic patients and is often associated with a conjunctivitis.\textsuperscript{27,32}
• Herpes simplex viruses types 1 and 2 are less commonly associated with NGU (2–3%).\textsuperscript{27,33}
• N. meningitidis, Haemophilus sp., Moraxella catarrhalis, Streptococcus sp., Candida sp., urethral stricture and foreign bodies have all been reported in a few cases and probably account for a small proportion of NGU;\textsuperscript{34}
• Urethritis, without an observable discharge, may have a different aetiology from symptomatic urethritis, with C. trachomatis\textsuperscript{12,35,36} and M. genitalium being detected less frequently,\textsuperscript{23,25,37} and in lower quantities.\textsuperscript{38,39} There is also a possible association between asymptomatic NGU and bacterial vaginosis.\textsuperscript{40,41}

It is assumed that the aetiological agents of gonorrhoea and sexually acquired male NGU could potentially cause complications in the female partner. Gonococcal and chlamydial infection and possibly M. genitalium\textsuperscript{6,42–44} have been implicated in upper genital tract inflammation in women, in particular pelvic inflammatory disease (PID - level of evidence III). This remains to be substantiated for pathogen-negative NGU. Asymptomatic chlamydia-negative NGU was reported in male partners of women with PID,\textsuperscript{45} but M. genitalium was not tested for in this study.

Clinical symptoms
• Urethral discharge;
• Dysuria;
• Urethral itching;
• Penile irritation;
• Nil.

CLINICAL SIGNS
• Urethral discharge. This may not have been noticed by the patient or may only be present on urethral massage (which should be done by the patient). The urethral discharge tends to be more profuse and purulent in gonorrhoea compared with NGU but this difference is not specific;
• Normal examination.

COMPLICATIONS AND CONSEQUENCES
• Sexually acquired reactive arthritis/Reiter’s syndrome;
• Increased genital shedding of HIV.

DIAGNOSIS AND INVESTIGATIONS

If microscopy is available, the diagnosis of urethritis can be confirmed by demonstrating PMNLs in the anterior urethra. This can be done by means of:

• A Gram-stained urethral smear containing \(\geq5\) PMNL per high-power (\(\times1000\)) microscopic field (averaged over 5 fields with greatest concentration of PMNLs)\textsuperscript{53} (III, B);
• A methylene blue-stained urethral smear containing \(\geq5\) PMNL per high-power microscopic field\textsuperscript{12,46} (III, B);
• Alternatively the FPU can be centrifuged and the pellet Gram stained. Urethritis is present if \(\geq10\) PMNL per high-power (\(\times1000\)) microscopic field (averaged over 5 fields with greatest concentration of PMNLs) is found. (III, B);
• Either urethral smear or FPU can be used: both tests will identify cases missed by the other test\textsuperscript{12} (IIb, B);
• The quality of the smear is heavily dependent on how the smear is taken and there is both inter- and intra-observer variation\textsuperscript{5,4} (IIb, B);
• Either a 5 mm plastic loop or cotton-tipped swab can be used and should be introduced 0.5 cm into the urethra (III, B). There are no published data comparing the two but the former is probably less traumatic to the patient (IV, C). A blunt metal curette may also be used\textsuperscript{46} (III, B);
• A leukocyte esterase test on the first void urine is too unreliable to be of use in clinical practice for diagnosis of urethritis (IIb, B). It remains useful for detecting urinary tract infection on the mid-stream urine;
• In the presence of overt discharge, urethral smear is a better choice than FPU: it will check for diplococci and other bacteria and in most of the situations will confirm the excess of PMNLs. T. vaginalis is better seen on a wet-mount examination (IV, C);
• There is controversy as to the value of microscopy in asymptomatic patients or in the absence of discharge.\textsuperscript{10,12,47} A single nucleic acid amplification test (NAAT) for C. trachomatis may miss up to 3% of men with urethral chlamydia,\textsuperscript{48} and a single NAAT for M. genitalium can miss 5–6% of asymptomatic men infected with M. genitalium.\textsuperscript{7,10,16} But relying on microscopy alone to select patients in whom to perform NAAT would miss up to 37% of C. trachomatis and up to 62% of M. genitalium urethral infections,\textsuperscript{8,11,12,22,25} although in some hands the performance of microscopy may be better\textsuperscript{23,30} (III, B). It seems wise unless the level of compliance of the patient population is very high and a reliable microbiological diagnosis is available, (chlamydia and ideally M. genitalium) to treat all asymptomatic patients whatever the results of microscopy (IV, C). Microscopy remains an important test in symptomatic men for the diagnosis of gonococcal urethritis (IV, C);
• The sensitivity of the smear test, but probably not the FPU\textsuperscript{49} is affected by the period since last passing urine (III, B). The optimum time to ensure a definite diagnosis in a symptomatic man is not known. Two to four hours is conventional;
• All patients attending should have a test for N. gonorrhoeae either by culture of urethral smear or by NAAT (IIa, B). If a NAAT is used a positive test should be confirmed by either culture or a different NAAT because of possible false positives.

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|l|l|l|}
\hline
Study & Nature & CT & Mg & TV & Other & No pathogen \\
\hline
Bradshaw et al.\textsuperscript{27} & Only symptomatic & 20 & 9 & 1 & 7 & 63 \\
Falk et al.\textsuperscript{7} & \(>10\) PMN/hpf & 22.5 & 12.5 & 65 & \textsuperscript{34} \\
Anagirus 2005\textsuperscript{18} & 7.4 & 8.3 & 84.3 & \textsuperscript{19} \\
Geisler 2005\textsuperscript{11} & 27 & Not done & 73 & \textsuperscript{12} \\
Marazzo 2000\textsuperscript{1} & 17 & Not done & 83 & \textsuperscript{13} \\
Leung et al.\textsuperscript{13} & Urethritis & 20.9 & 10.9 & 65 & \textsuperscript{14} \\
\hline
\end{tabular}
\caption{Individual detection rates (percent) of more common organisms in recent studies}
\end{table}
The importance of their sex partner(s) being evaluated and treated; ofloxacin 200 mg twice a day or 400 mg once a day for seven days (Ib, A).

- Erythromycin 500 mg twice daily for seven days (Ib, A).

TETRACYCLINES AND AZITHROMYCIN ARE GENERALLY EFFECTIVE AGAINST C. TRACHOMATIS THOUGH SPORADIC REPORTS OF TREATMENT FAILURE HAVE BEEN REPORTED WITH TETRACYCLINES.54 While in general treatments that are effective against C. trachomatis appear to be also effective in NGU, tetracyclines and azithromycin in the doses used do not consistently eradicate M. genitalium.55–58 (IIa, B).

All patients should be offered tests for HIV and syphilis.

RECOMMENDED REGIMENS FOR NGU
Choice of regimens depends on availability – both treatments are equally effective (Ib, A)

- Azithromycin 1 g orally in a single dose (Ib, A);

or

- Doxycycline 100 mg twice a day for seven days (Ib, A).

ALTERNATIVE REGIMENS
- Erythromycin 500 mg twice daily for seven days (Ib, A);

or

- Ofloxacin 200 mg twice a day or 400 mg once a day for seven days (Ib, A).

Single-dose therapy has the advantage of improved compliance, although azithromycin has not been shown to be more effective in clinical studies than doxycycline (apart from M. genitalium infection) (IIa, B).

SEXUAL CONTACTS/PARTNERS
All sexual partners at risk should be assessed and offered treatment without waiting for microbiological diagnosis, maintaining patient confidentiality. The duration of ‘look back’ for treating previous partners is arbitrary and should be tailored to the sexual history; three months is suggested (IV, C). If C. trachomatis or N. gonorrhoeae is detected, it is important to ensure that all sexual partner(s) potentially at risk are notified (IV, C). Partner(s) notification and management should be carried out with sensitivity, considering socio-cultural issues and avoiding stigma and violence.

- Details of all contacts should be obtained at the first visit. Consent should also be obtained so that if C. trachomatis or N. gonorrhoeae is detected and the index patient does not re-attend, he can be contacted and/or provider referral can be initiated for sexual contacts (IV, C);
Female contacts of men with gonococcal or chlamydial urethritis should be treated empirically (IIb, B).

There is no direct evidence of treatment benefit to partners of men with chlamydia-negative NGU. There are, however, a number of issues that may influence decision-making.

(a) NGU cohort studies have looked at the effect on response of urethritis and have produced conflicting conclusions;34,59
(b) There are reports of patients with persistent or recurrent urethritis being cured only after their sexual partner received antibiotic treatment;40
(c) Even newer NAATs may miss 3–10% of chlamydia-positive individuals;
(d) There is also discordance in the isolation of chlamydia between partners;19,61
(e) C. trachomatis can clear without treatment from the cervices of women62,63 though much less frequently from the urethras of men;64
(f) Finally,65–67 M. genitalium accounts for approximately 20% of cases of NGU and probably causes disease in women.6,44

In the absence of randomized prospective studies it would be prudent to treat partners of microorganism-negative NGU concurrently to potentially reduce female morbidity (IV, C).

FOLLOW-UP FOR PATIENTS WITH NGU

Follow-up after 2–3 weeks is important in order to assess compliance with therapy, ensure resolution of symptoms and to assess the risk of re-infection from an untreated partner, particularly in chlamydia-positive patients. The follow-up interview can be performed by phone or other means of communication or in person68,69 (III, B). Patients who remain asymptomatic, who have not completed their medication or who have had unprotected sexual intercourse with an untreated partner should be asked to return to the clinic and re-treated with appropriate contact tracing (IV, C).

A test of cure in NGU in an otherwise asymptomatic individual is not recommended (III, B).

PERSISTENT/RECURRENT NGU

There is no consensus of opinion for either the diagnosis or the management of this condition. It is empirically defined as persistent or recurrent symptomatic urethritis occurring 30–90 days following treatment of acute NGU70 and occurs in 10–20% of patients.70–73
Its aetiology is probably multifactorial.34,59,70 M. genitalium may be implicated in 20–40%57,70 and the current treatments for NGU do not always eradicate this organism.55,57,58 In a randomized study of 398 men, 1 g of azithromycin resulted in failure in 16% and doxycycline 100 mg twice a day for seven days in 64% of those who returned for follow-up.56
In two small open-labelled studies azithromycin 500 mg stat followed by 250 mg daily for the next four days or moxifloxacin 400 mg daily for 10 days cured all patients.57,74 In a retrospective survey, Jernberg et al.25 had a success rate of 79% with azithromycin (1 g single dose as effective as 5 days 'course) and 100% with moxifloxacin 400 mg daily for seven days. Because of possible higher risk of resistance after a single dose of azithromycin, some experts recommend a five days' course for treatment of M. genitalium (IIa, B). Recent report of severe hepatotoxicity and Stevens–Johnson syndrome in a minority of patients receiving moxifloxacin should also be taken into account.76 A role for U. urealyticum in chronic NGU has also been suggested.77 Although this organism may also exhibit tetracycline resistance, the therapeutic implications remain unclear. Any treatment of chronic NGU should cover M. genitalium 78 (III, B) and T. vaginalis (in areas where it is prevalent – IV, C). The only randomized controlled trial for chronic NGU showed that erythromycin for three weeks is better than placebo,79 but the study did not test for M. genitalium, nor included treatment of partners;

In the absence of evidence of benefit, female partners of men with persistent/recurrent NGU do not need to be retreated if treated appropriately at first with any of the first-line treatments discussed previously (IV, C). However, in view of the emerging evidence that both doxycycline and azithromycin can fail to eradicate M. genitalium in men, it is likely that this is also the case in women. This, therefore, is an area where further research is needed.

MANAGEMENT OF PERSISTENT/RECURRENT NGU

Ensure that the patient has completed the initial course of therapy and that reinfection is not a possible cause;
Only treat if patient has definite symptoms of urethritis, or physical signs on examination. Reassure asymptomatic patients that no further test or treatment is necessary.

RECOMMENDED REGIMENS

Patient symptomatic or an observable discharge present.55,70,79–81
First-line treatment

Azithromycin 500 mg stat then 250 mg for the next four days (IIa, B).
Plus metronidazole 400–500 mg twice daily for five days (IV, C).*

or

Erythromycin 500 mg four times daily for three weeks (IIb, A).
Plus metronidazole 400–500 mg twice a day for five days (IV, C).*

Second-line regimens

Moxifloxacin 400 mg once daily for 7–10 days (III, B),74
Plus metronidazole 400–500 mg twice daily for five days (IV, C).*

* In areas where T. vaginalis is prevalent.

There are no trials comparing the three regimens and the situation may be quite different in different settings, depending on the microbiological resistance of M. genitalium to...
tetracyclines and macrolides. In general, it is advisable not to use a macrolide for second-line treatment if azithromycin 1 g stat was used for first-line treatment (IV, C).

Continuing symptoms

There is only limited evidence on how best to manage patients who either remain symptomatic following a second course of treatment or who have frequent recurrences after treatment.

- Urological investigation is usually normal unless the patient has urinary flow problems79 and is not recommended (IV, C);
- Chronic abacterial prostatitis and psychosexual causes should be considered in the differential diagnosis but are rare79–81 (IV, C);
- For men with persistent or recurrent urethritis, there is currently no evidence that re-treatment of an appropriately treated sexual partner is beneficial (see above) (IV, C);
- Reassurance can be given that continuing symptoms have not been associated with serious long-term physical morbidity (IV, C);
- Symptoms tend to improve slowly after many months. Simple analgesics, non-steroidal anti-inflammatory and anxiolytic drugs are sometimes helpful in relieving symptoms. (IV, C).

Auditable outcome measures

- Symptomatic men should be offered microscopy of a Gram-stained urethral smear or first void urine (95%);
- Men with NGU should be offered treatment with a recommended antibiotic regimen (95%).

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(Reviewed 9 April 2009)

**APPENDIX**

**LEVELS OF EVIDENCE AND GRADING OF RECOMMENDATIONS**

**Levels of evidence**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomized controlled trials.</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomized controlled trial.</td>
</tr>
<tr>
<td>Ia</td>
<td>Evidence obtained from at least one well-designed study without randomization.</td>
</tr>
<tr>
<td>Ia</td>
<td>Evidence obtained from at least one other type of well-designed quasi-experimental study.</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies and case control studies.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.</td>
</tr>
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</table>

**Grading of recommendations**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Levels</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ia, Ib</td>
<td>Requires at least one randomized controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.</td>
</tr>
<tr>
<td>B</td>
<td>IIa, IIb, III</td>
<td>Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendation.</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.</td>
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</table>