2009 European Guideline on the management of non-gonococcal urethritis

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Introduction

Urethritis, or inflammation of the urethra, in men is characterised 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 leucocytes (PMNLs) in the anterior urethra. This is usually assessed using a urethral smear, but a first-pass urine specimen (FPU) can also be used. Urethritis is described as either gonococcal, when *Neisseria gonorrhoeae* is detected, or non-gonococcal (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* [1], although female NGU due to *C. trachomatis* and *Mycoplasma genitalium* has been reported[2].

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. [3;4] In many men with urethritis a known pathogen is not isolated [5-8]. Up to 1/3 of men infected with either *C. trachomatis* or *M. genitalium* will not have an excess of PMNLs [7;9-13], the sensitivity of smear ($\geq$ 5 PMNLs) being far better in the case of an overt discharge, variations being furthermore dependent on populations and techniques of sampling. Indeed if a discharge is present, the isolation rate of *C. trachomatis* or *M. genitalium* reaches 50%.[7;12;14;15]. In 3-20% an undiagnosed *C. trachomatis* or *M. genitalium* infection is found in the partner of a patient with non-chlamydial, non-*Mycoplasma genitalium* urethritis if he or she is tested.[7;16-19]

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 to more affluent neighbourhoods. [20;21] 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.[7;13]
- Chlamydia is more likely to be isolated in younger patients than *M. genitalium*[22] and the two organisms rarely coexist in the same individual. [6;23]

- In 30-80% of the cases with NGU neither *C. trachomatis* nor *M. genitalium* is detected. [5-8;11;24-27]
- 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. [28]. *T. vaginalis* isolation is greater in men >30 years [29].
- The exact role of ureaplasmas in NGU has been controversial, due to the conflicting observations in clinical studies. Ureaplasmas are ubiquitous micro-organisms which can be isolated from 30-40 % 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. [30]
- A urinary tract infection may account for 6.4% (95% CI 1.5% - 11.3%) of cases of NGU, although there is only one study evaluating this. [31]
- Adenovirus infection may account for perhaps 2-4% of cases of symptomatic patients and is often associated with a conjunctivitis. [27;32]
- Herpes simplex viruses types 1 and 2 are less commonly associated with NGU (2-3%)[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[34].
- Urethritis, without an observable discharge, may have a different aetiology from symptomatic urethritis, with *C. trachomatis*[12;35;36] and *M. genitalium* being detected less frequently,[23;25;37] and in lower quantities[38;39]. There is also a possible association between asymptomatic NGU and bacterial vaginosis. [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*[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,[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

- Epididymo-orchitis with impairment of male fertility
- 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 by means of:

- A Gram-stained urethral smear containing ≥ 5 PMNL per high-power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs) [35] (**III, B**)
- A methylene blue-stained urethral smear containing ≥ 5 PMNL per high-power microscopic field [7;46] (**III, B**)

- Alternatively the first passed urine (FPU) can be centrifuged and the pellet Gram stained . Urethritis is present if ≥ 10 PMNL per high-power (x1000) microscopic field (averaged over five 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 [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. [3;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 [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. *Trichomonas 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. [10;12;47] .A single nucleic acid amplification test (NAAT) for *C.trachomatis* may miss up to 3% of men with urethral chlamydia [48] and a single NAAT for *M.genitalium* can miss 5-6% of asymptomatic men infected with *M. genitalium*. [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, [8;11;12;22;25] although in some hands the performance of microscopy may be better.[23;38] (**III, B**) It seems wise unless the level of compliance of the patient population is very high and a reliable microbiological diagnosis available, (chlamydia and ideally *M. genitalium*) to treat all symptomatic 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[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. 2-4 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 in low-prevalence populations as well as establishing antibiotic sensitivity. [see gonorrhoea guidelines].
- *C. trachomatis* should also be sought (see guideline on chlamydia). It should be noted that even a NAAT will miss between 3%[48] and 10% of infections [50-52]. (**III, B**)
- Commercial tests for *M. genitalium* are not widely available and the place of such tests in routine clinical practice needs to be determined.
- A mid-stream urine should be taken if a urinary tract infection is suspected from the history such as, for example, if the patient complains of severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency, or has not been sexually exposed. In one study a dipstick incorporating nitrite and leukocyte esterase tests had a sensitivity and specificity for urinary tract infection of 83 and 90% respectively.[31](**III, B**)
- The traditional two-glass urine test adds little to the diagnosis and should be abandoned (**IV, C**).

Management

General advice (IV, C)

The following should be discussed and clear written information provided:

- An explanation of the causes of urethritis, including non-infective causes, and possible short term and long term implications for the health of the patient and his partner.
- The side-effects of treatment and the importance of complying fully with it.
- The importance of their sex partner(s) being evaluated and treated
- Advice to abstain from sexual intercourse, or if that is not acceptable, the consistent use of condoms (also for oral and anal sex) until he has completed therapy and his partner(s) have been treated.

- Advice on safer sex and consistent use of condoms.
- The importance of complying with any follow-up arrangements made.

Treatment

- Treatment should be initiated as soon as the diagnosis of NGU is made and without waiting for the results of tests for chlamydia and cultures for *N. gonorrhoeae*. Treatment should be given to all symptomatic patients even if the microscopy is non-diagnostic. (**IV, C**)

In situations where microscopy is not available or results are unreliable, management should be syndromic with treatments that cover both *C trachomatis* and *N gonorrhoeae*, and in areas of high prevalence *T. vaginalis* (for more details on syndromic management see WHO guidelines http://www.who.int/reproductive-health/publications/mngt_stis/index.html) . The inclusion of treatment for *N gonorrhoeae* should only be routine if there is a discharge, as male gonorrhoea in the absence of discharge is uncommon. It would also depend on the prevalence of the infection in the community. (**IV, C**) Ideally, treatment should be effective (microbiological cure rate for *C. trachomatis* >95%), easy to take (not more than twice daily), with a low side-effect profile, and minimal interference with daily life. (**IV, C**) However assessing treatment efficacy is problematic, as no pathogen is identifiable in the majority of cases, and the inflammatory process may not reflect persistent infection [34] It is important to note that the inflammatory exudate may persist for a variable length of time even when the putative organism has been eliminated. [53] Venereophobia is a classical cause of urethral discharge, induced by regular squeezing: in that particular case, the absence of PMNLs on examining the urethral smear or FPU must discourage giving recurrent antibiotic treatments.

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 1g orally in a single dose (**Ib, A**)

  or

- Doxycycline 100 mg twice a day for 7 days (**Ib, A**)

Alternative regimens

- Erythromycin 500mg twice daily for 14 days (**Ib, A**)

  or

- Ofloxacin 200mg twice a day or 400mg once a day for 7 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; 3 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 reattend, 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 which may influence decision making.

a. NGU cohort studies have looked at the effect on response of urethritis and have produced conflicting conclusions. [59]

b. There are reports of patients with persistent or recurrent urethritis being cured only after their sexual partner received antibiotic treatment. [60]

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 women[62;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 randomised 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 reinfection 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 person[68;69] (**III, B**). Patients who remain symptomatic, 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 NGU [70] 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 randomised study of 398 men azithromycin 1g resulted in failure in 16% and doxycycline 100mg d 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 4 days or moxifloxacin 400 mg daily for 10 days cured all patients[57;74] In a retrospective survey Jernberg et al had a success rate of 79 % with azithromycin (1g single dose as effective as 5 days ' course) and 100 % with moxifloxacin 400 mg daily for 7 days[75]. Because of possible higher risk of resistance after a single dose of azithromycin , some experts recommend a 5 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 randomised controlled trial for chronic NGU showed that erythromycin for three weeks is better than placebo,[79] but the study did not tested 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 500mg stat then 250mgs for the next 4 days (**IIa, B**)
  Plus metronidazole 400-500 mg twice daily for 5 days (**IV, C**) *

  or
- Erythromycin 500 mg four times daily for 3 weeks [79](**Ib, A**)
  Plus metronidazole 400-500 mg twice a day for 5 days (**IV, C**).*

Second line regimens

- Moxifloxacin 400mg once daily for 7 -10 days **(III, B)**[74]
  Plus metronidazole 400-500 mg twice daily for 5 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 microbiologic 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 problems[80] and is not recommended. (**IV, C**)
- Chronic abacterial prostatitis and psychosexual causes should be considered in the differential diagnosis but are rare. [79-81] (**IV, C**)
- For men with persistent or recurrent urethritis, there is currently no evidence that retreatment 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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Conflict of interests

None.

Rigor of development

MEDLINE searches for 1970 to present using MeSH headings “urethritis” including all documents and subheadings. Additional searches were conducted using MeSH headings “Non-gonococcal urethritis”, “nongonococcal urethritis”, “ non-specific urethritis”, “NGU”, “NSU”, “Chlamydia trachomatis” “Mycoplasma genitalium”.

The Cochrane library for 1970 to the present using keywords “Non-gonococcal urethritis”, “nongonococcal urethritis”, “non-specific urethritis”, “NGU”, “NSU”. Hand search conference proceedings – BASHH (MSSVD), ISSTDR

Table 1. Prevalence of the most common pathogens detected from patients with NGU

Micro-organism	**Prevalence**	**Reference**
C. trachomatis	11-43%	{7;8;11;12;16;19;23-25;27;82}
M. genitalium	9-25%	{5-7;12;13;16;22;23;25;27;38;83;84}
Adenoviruses	2-4%	27;32
T. vaginalis	1- 20%	28;82;85-87
Herpes simplex virus	2-3%	27;33

Table 2. Individual detection rates (percent) of more common organisms in recent studies.

Study	Nature	CT	Mg	TV	Other	No pathogen
Bradshaw 2006[27]	Only symptomatic	20	9	1	7	63
Falk 2004[7]	>10 PMN/hpf	22.5	12.5			65
Angarius 2005[16]		7.4	8.3			84.3
Giesler 2005[11]		27	Not done			73
Marazzo 2000[1]		17	Not done			83
Leung 2006[13]	Urethritis	20.9	10.9			65

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Appendix 1

Levels of evidence and grading of recommendations

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials.

Ib Evidence obtained from at least one randomised controlled trial.
IIa Evidence obtained from at least one well designed study without randomisation.
IIb Evidence obtained from at least one other type of well designed quasi-experimental study.
III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies.
IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.
Grading of Recommendations
A (Evidence levels Ia, Ib)
Requires at least one randomised control trial as part of the body of literature of overall good
quality and consistency addressing the specific recommendation.
B (Evidence levels IIa, IIb, III)
Requires availability of well conducted clinical studies but no randomised clinical trials on the
topic of recommendation.
C (Evidence IV)
Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.