

2007 UK National Guideline on the Management of Non-gonococcal Urethritis

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British Association for Sexual Health and HIV
Clinical Effectiveness Group

Scope and purpose

The main objective is to reduce the number of sexually transmitted infections (STIs) and the complications that can arise in people either presenting with signs and symptoms of an STI, or undergoing investigation for possible infection.

Specifically, this guideline offers recommendations on the diagnostic tests, treatment regimens and health promotion principles needed for the effective management of Non-Gonococcal Urethritis (NGU), covering, the management of the initial presentation, as well as how to prevent transmission and future infection.

It is aimed primarily at people aged 16 years or older (see specific guidelines for those under 16) presenting to health care professionals, working in departments offering level 3 care in STI management (see national strategy¹) within the United Kingdom. However, the principles of the recommendations should be adopted across all levels (levels 1 and 2 may need to develop, where appropriate, local care pathways).

The recommendation of this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.

Stakeholder involvement

The document was reviewed by the Bacterial Special Interest Group and the Clinical Effectiveness Group of BASHH, and their comments incorporated. It was subsequently circulated for comments by the BASHH membership for three months.

What is new?

- No need to do a urethral smear in asymptomatic men.
 - First line treatment for NGU is Azithromycin 1 g orally as a single dose
 - The follow-up interview can be performed by telephone
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- Persistent/recurrent NGU occurs in 10-20% of patients.
 - A urethral smear should only be performed on follow-up if the patient is symptomatic.
 - Any treatment for persistent/recurrent NGU should cover *Mycoplasma genitalium* and *Trichomonas vaginalis*.
 - In persistent / recurrent cases, Moxifloxacin is no longer recommended as a 1st line therapy due to recent safety concerns from the UK Medicines and Healthcare products Regulatory Agency⁸⁴. It is now placed as a 2nd line therapy (see main text)
 - The 1st line treatment for persistent /recurrent NGU is
Azithromycin 500mg stat, then 250mg daily for next 4 days, plus
Metronidazole 400mg twice daily for 5 days
OR
Erythromycin 500mg four times daily for 3 weeks, plus
Metronidazole 400mg twice daily for 5 days
 - The two-glass urine test should be abandoned.

Introduction

Urethritis, or inflammation of the urethra, is a multifactorial condition which can be sexually acquired. It is characterised by discharge and/or dysuria but may be asymptomatic. The diagnosis of urethritis is confirmed by demonstrating an excess 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. The term non-specific urethritis (NSU) applies to non-gonococcal non-chlamydial NGU and to avoid confusion should be avoided. Mucopurulent cervicitis is the female equivalent with approximately 40% of cases being due to infection with *Chlamydia trachomatis*.²

There are a number of uncertainties with NGU. Urethral inflammation can occur without a known pathogen being isolated in the majority of patients even using more sensitive detection methods³⁻⁶. Conversely 8-37% of men infected with either *C. trachomatis* or *Mycoplasma genitalium* will have not have the diagnostic criteria on Gram stain of the urethral exudates.^{5;7-10} Limiting tests to men with discharge or dysuria increases isolation of *C. trachomatis* or *M. genitalium* to up to 50%.^{5;11;12} In a further 3-20% an undiagnosed *C. trachomatis* or *M. genitalium* is found in the partner if he/she is tested.^{5;13-16} Finally inter-observer and intra-observer error, especially in samples with low grade inflammation (5-20 PMNL/hpf), make diagnostic consistency difficult.^{17;18}

Aetiology

The prevalence of the common organisms associated with NGU is listed in table 1.

The commonest organisms implicated are *C. trachomatis* and *M. genitalium* with the latter perhaps causing more symptoms.^{5;19} The isolation rates of common organisms in more recent studies using modern diagnostic tests is shown in table 2.

- Chlamydia is more likely to be isolated in younger patients than *M. genitalium*²⁰ and the two organisms rarely coexist in the same individual.⁴
- In 30-80% of the cases with NGU neither *C. trachomatis* nor *M. genitalium* is detected.^{3-6;10;21-24}
- 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 greatly increased with the use of more sensitive polymerase chain reaction assays.²⁵ *T. vaginalis* isolation is greater in men >30 years²⁶.
- The exact role of ureaplasmas in NGU has been controversial due to the conflicting observations in clinical studies. Ureaplasmas are ubiquitous micro-organisms which have recently been divided into two biovars: *U. urealyticum* biovar 2 may account for 5-10% of cases of acute NGU.²⁷
- A urinary tract infection may account for 6.4% (95% CI 1.5% - 11.3%) of cases, although there is only one study evaluating this.²⁸
- Adenoviruses may account for perhaps 2-4% of symptomatic patients and is often associated with a conjunctivitis.^{24;29}
- Herpes simplex viruses types 1 and 2 are less commonly associated with NGU (2-3%)^{24;30}

- *N. meningitidis*, *Haemophilus sp.*, *Candida sp.*, urethral stricture and foreign bodies have been reported in a few cases and probably account for a small proportion of NGU³¹.
- Asymptomatic urethritis, without an observable discharge, may have a different aetiology from symptomatic urethritis, with *C. trachomatis*³²⁻³⁴ and *M. genitalium* being detected less frequently^{22;35}, and at lower quantities^{36;37}. There is also a possible association of asymptomatic NGU with bacterial vaginosis.^{38;39}

It is assumed that the aetiological agents of sexually acquired male NGU could potentially cause genital tract inflammation in women, in particular pelvic inflammatory disease (PID). This is undoubted with chlamydial and gonococcal infection and possible with *M. genitalium*^{4;40-42} but remains to be substantiated for pathogen-negative NGU. Asymptomatic chlamydia-negative NGU was reported in male partners of women with PID,⁴³ but *M. genitalium* was not tested for in that study.

Clinical features*

SYMPTOMS

- Urethral discharge
- Dysuria
- Penile irritation
- Nil

SIGNS

- Urethral discharge. This may not have been noticed by the patient or may only be present on urethral massage.
- Normal examination

Examining the FPU for casts is of little additional value (IV)

COMPLICATIONS

- Epididymo-orchitis
- Sexually acquired reactive arthritis / Reiter's syndrome

These are infrequent, occurring in fewer than 1% of cases though incomplete forms may be more common.

Diagnosis

The diagnosis of urethritis must be confirmed by demonstrating PMNLs in the anterior urethra. This can be by means of:

(i) A Gram stained urethral smear containing ≥ 5 PMNL per high-power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs) ³² *and/or*

(ii) A Gram stained preparation from a centrifuged sample of a first passed urine (FPU) specimen, containing ≥ 10 PMNL per high-power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs).

- Either test can be used: both tests will identify cases missed by the other test ³⁴
- The quality of the smear is heavily dependent on how the smear is taken and there is both inter- and intra-observer variation. ^{17;18}
- Either a 5 mm plastic loop or cotton-tipped swab can be used and should be introduced about 1 cm into the urethra. There are no published data comparing the two but the former is probably less traumatic to the patient (IV).
- Positive leucocyte esterase activity on dipstick on FPU specimen correlates with NGU and the detection of chlamydia ²¹ and is considered diagnostic by some authorities. ⁴⁴ However, it does not have adequate sensitivity to be considered a reliable rapid diagnostic test for acute

NGU^{45;46}. Moreover its positive predictive value for *C. trachomatis* in asymptomatic patients is poor.²¹

- There is controversy as to the need to perform microscopy in asymptomatic patients.^{8;47} Treatment will be delayed in up to 30% of those infected with *C. trachomatis* who are asymptomatic^{8;14;16;48}. Also a single nucleic acid amplification test (NAAT) may miss up to 3% of men with urethral chlamydia⁴⁹ and will miss 5-6% of asymptomatic men infected with *M. genitalium*.^{7;8;13} It is however, unclear if microscopy would identify a substantial proportion of these patients, nor is *M. genitalium* currently proven to cause serious pathology (such as pelvic inflammatory disease). On the other hand, omitting microscopy in asymptomatic men will prevent diagnosing 77-87% of men as having a sexually transmitted infection in whom neither of the above organisms will be isolated^{10;13}. Indeed, relying on microscopy alone will miss up to 37% of *C. trachomatis* and up to 23% of *M. genitalium* urethral infections.^{6;10;20;22} There is, therefore, little justification in performing urethral microscopy in asymptomatic men (IIB). It does of course remain an important test in symptomatic men for the diagnosis of gonococcal urethritis.

- While a leucocyte esterase test (1+ = positive) has variable sensitivity in diagnosing urethritis it has a high negative predictive value (>96-8%), similar to that of a urethral smear, in asymptomatic men for the detection of *N. gonorrhoeae* and *C. trachomatis* and thus probably *M. genitalium*.^{21;45} However its positive predictive value for chlamydia in asymptomatic men is low (5.1-23.3%).²¹ It therefore has little place in routine practice though its good negative predictive value may be useful in population screening for *C. trachomatis*.²¹

- Physical examination of asymptomatic men does not result in an increased diagnosis of urethral pathogens⁵

- The sensitivity of the smear test, but probably not the FPU⁵⁰ is affected by the period since last passing urine. The optimum time to ensure a definite diagnosis in a symptomatic man is not known. 2-4 hours is conventional.
- Symptomatic patients, in whom no discharge or urethritis is detected, could either be retested having held their urine overnight, (IV) or given empirical treatment (IV). With the latter choice empirical treatment to the partner(s) would be indicated.

Investigations

- All patients attending should have a test for *N. gonorrhoeae*. If a NAAT is used for *N. gonorrhoeae* a positive test should be confirmed by culture. [see BASHH gonorrhoea guidelines].
- *C. trachomatis* should also be sought (see BASHH guideline on chlamydia). It should be noted that even a NAAT will miss between 3%⁴⁹ and 10% of infections⁵¹⁻⁵³.
- Commercial testing for *M. genitalium* is not available and the place of such tests in routine clinical practice, once they become available, needs to be determined.
- An MSU should be taken if a urinary tract infection is suspected. 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 using a dipstick incorporating nitrite and leucocyte esterase tests had a sensitivity and specificity for urinary tract infection of 83 and 90% respectively.²⁸
- The traditional two-glass test adds little to the diagnosis and should be abandoned [IV].

Management

GENERAL ADVICE

The following should be discussed and clear written information provided:

- An explanation of the causes of NGU, 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, until he has completed therapy and his partner(s) have been treated. [IV]
- Advice on safer sex
- The importance of complying with any follow-up arrangements made.

Treatment

Treatment should be initiated as soon as the diagnosis is made and without waiting for the results of tests for chlamydia and cultures for *N. gonorrhoeae*. 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 cause minimal interference with daily lifestyle. However assessing treatment efficacy is problematic, as no pathogen is identifiable in over 60% of cases, and the inflammatory process may not reflect persistent infection³¹ It is important to note that the inflammatory exudate may persist for an unknown length of time even when the putative organism has been eliminated.⁵⁴

Tetracyclines are generally effective against *C. trachomatis* though sporadic reports of treatment failure have been reported.⁵⁵ While in

general treatments that are effective against *C. trachomatis* appear to be also effective in NGU, tetracyclines in the doses used do not consistently eradicate *M. genitalium*⁵⁶⁻⁵⁸ and this may also be the case with azithromycin 1g stat^{57;58} (see below).

RECOMMENDED REGIMENS (GRADE OF RECOMMENDATION A)

- Azithromycin 1g orally in a single dose (Ib)
or
- Doxycycline 100 mg twice a day orally for 7 days (Ib)

ALTERNATIVE REGIMENS (A)

- Erythromycin 500mg twice daily for 14 days (Ib)
or
- Ofloxacin 200mg twice a day or 400mg once a day for 7 days (Ib)

COMPLIANCE WITH THERAPY

Single dose therapy has the advantage of improved compliance although azithromycin has not been shown to be more effective in clinical studies than doxycycline.

Sexual contacts/partners

All sexual partners at risk should be assessed and offered epidemiological treatment, maintaining patient confidentiality. The duration of “look back” is arbitrary; 4 weeks is suggested for symptomatic men (IIb).

- If *C. trachomatis* or *N. gonorrhoeae* are detected it is important to ensure that all sexual partner(s) potentially at risk have been notified (see relevant guidelines).
- Details of all contacts should be obtained at the first visit. Consent should also be obtained so that if *C. trachomatis* or *N. gonorrhoeae* are detected subsequently and the index patient does not reattend, he can be contacted and/or provider referral can be initiated for sexual contacts (IV).
- Female contacts of men with chlamydial urethritis should be treated regardless of the results of tests for chlamydia (Ib).

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 appropriate 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.^{16;61}
- e. *C. trachomatis* can clear without treatment from the cervixes 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 and probably causes disease in women.^{4;42}

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).

Follow-up for patients with NGU

Follow up is important in order to assess compliance with therapy – particularly in chlamydia-positive patients. The follow up interview can be performed by phone. 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)

Persistent/recurrent NGU

This is empirically defined as persistent or recurrent symptomatic urethritis occurring 30-90 days following treatment of acute NGU ⁶⁸ and occurs in 10-20% of patients. ⁶⁸⁻⁷¹ There is no consensus of opinion for either the diagnosis or the management of this condition. Its aetiology is probably multifactorial. ^{31;59;68} *M. genitalium* may be implicated in 20-40% ^{58;68}. Tetracyclines, two weeks of erythromycin or a single dose of azithromycin do not reliably eradicate this organism ^{56;58}. In a randomised study of 398 men azithromycin 1g resulted in failure in 16% and doxycycline 100mgs bd for seven days in 64% of those who returned for follow-up. ⁵⁷ In an open Scandinavian study azithromycin 500 mgs stat followed by 250 mg daily for the next 4 days cured all of 19 patients ⁵⁸. A role for *U. urealyticum* in chronic NGU has also been suggested. ⁷². Although this organism may also exhibit tetracycline resistance the therapeutic implications remain unclear. Any treatment of chronic NGU should cover *M. genitalium* ⁷³ and *T. vaginalis* which are not covered by standard therapy (IV).

The only randomised controlled trial for chronic NGU showed that erythromycin for three weeks is better than placebo⁷⁴ but did not test for *M. genitalium*, nor include partners.

As there is no evidence that female partners of men with persistent/recurrent NGU are at increased risk of pelvic inflammatory disease, they do not need to be retreated if treated appropriately at first. 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 and this is therefore an area where further research is needed.

DIAGNOSIS OF PERSISTENT/RECURRENT NGU

- Avoiding routine test of cure in NGU will avoid creating a “patient” in an otherwise asymptomatic individual.

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 - (C)

Patient symptomatic or an observable discharge present^{56;68;74-76}

- **1st line**

- Azithromycin 500mg stat then 250mg for the next 4 days (IIIb)
plus Metronidazole 400 mg twice daily for 5 days (IV)

OR

Erythromycin 500 mg four times daily for 3 weeks ⁷⁴(Ib)
plus Metronidazole 400mg twice daily for 5 days (IV)

■ **2nd line**

Moxifloxacin 400mg orally once daily for 10 days (IIIb)⁷⁷
plus Metronidazole 400mg twice daily for 5 days (IV)

NB: In persistent / recurrent cases, Moxifloxacin is no longer recommended as a 1st line therapy due to recent safety concerns (an increased risk of life threatening liver reactions and other serious risks) from the UK Medicines and Healthcare products Regulatory Agency⁸⁴. It is now placed as a 2nd line therapy.

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 problems⁷⁵ and is not recommended.
- Chronic abacterial prostatitis (see guideline on prostatitis) and psychosexual causes

should be considered in the differential diagnosis. ⁷⁴⁻⁷⁶

- For men with persistent or recurrent urethritis, there is currently no evidence that retreatment of an appropriately treated sexual partner is beneficial (see above).

Auditable outcome measures

- Symptomatic men should be offered microscopy of a Gram-stained urethral smear or first void urine (100%).
- Men with NGU should be offered treatment with a recommended antibiotic regimen (100%).

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Membership of the CEG

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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), ISSTD

This document is an update of the original article :

Horner PJ, Shahmanesh M. National guideline for the management of non-gonococcal urethritis. *Sex Transm Inf* 1999;75 (Supp 1):S9-S12. Updated 2002, http://www.bashh.org/guidelines/2002/ngu_0901c.pdf

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

Micro-organism	Prevalence	Reference
<i>C. trachomatis</i>	11-43%	5;6;10;13;16;21;22;24;34;78
<i>M. genitalium</i>	9-25%	3-5;13;19;20;22;24;34;34;34;79;80
Adenoviruses	2-4%	24;29 }
<i>T. vaginalis</i>	1- 20%	25;78;81-83
Herpes simplex virus	2-3%	24;30

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

Study	Nature	CT	Mg	TV	Other	No pathogen
Bradshaw 2006 ²⁴	Only symptomatic	20	9	1	7	63
Falk 2004 ⁵	>10 PMN/hpf	22.5	12.5			65
Angarius 2005 ¹³		7.4	8.3			84.3
Giesler 2005 ¹⁰		27	Not done			73
Marazzo 2000 ²		17	Not done			83
Leung 2006 ¹⁹	Urethritis	20.9	10.9			65

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