2014 European Guideline on the management of non-gonococcal urethritis

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Guideline Development

This guideline has been updated by reviewing the previous European NGU (2009) guideline and conducting a comprehensive literature search of publications from 2008 to December 2013. MEDLINE was used to identify published articles including the search terms ‘nongonococcal urethritis’, ‘non-gonococcal urethritis’, ‘nonspecific urethritis’, ‘non-specific urethritis’ and broadened the search to include ‘urethritis’ and urethritis combined with ‘Chlamydia trachomatis’ or ‘Mycoplasma genitalium’. Reviews, case reports, editorials, comments, letters, research pertaining to the development of lab assays and the study of genomics were excluded. Due to the paucity of clinical trials all entries in the English language were reviewed, and if relevant the full text obtained.

Direct comparison of published studies is hindered by the majority lacking a clear microscopic definition of NGU, or using an alternative definition to ‘five or more polymorph leucocytes per high powered field averaged over five fields with the greatest concentration of polymorphs’ and varying specimen collections techniques. Due to scarcity of relevant high quality research these studies have been included despite their limitations.

The first draft of the guideline was prepared by PH and KB and reviewed by all co-authors. Consensus was used to resolve differences in expert opinion. PH and KB also co-authored the recently updated UK BASHH National NGU guideline which will shortly be available at http://www.bashh.org/BASHH/Guidelines/Guidelines/BASHH/Guidelines/Guidelines.aspx. A similar format has been used although there are differences in recommendations due to differences in expert opinion and variations in the epidemiology of some of the infectious causes of urethritis throughout Europe.
What is new in this updated guideline?

Aetiology

• The reported prevalence of *Mycoplasma genitalium* isolated from men with non-gonococcal urethritis has increased.

Diagnosis

• A urethral smear using a 5 mm plastic loop is less painful than a Dacron swab, which is less painful than a Rayon swab.
• If a symptomatic man has a negative urethral smear and leucocyte esterase dipstick, the patient can be reassured and advised to re-attend for an early morning smear if his symptoms do not settle. Empirical treatment without verifying the presence of urethritis is not recommended as there is a risk it may perpetuate their symptoms.
• Symptomatic patients should be referred to a centre which has microscopy available. When microscopy is not available, the presence of a mucopurulent or purulent urethral discharge on examination, \(\geq 1+\) on a leucocyte esterase dipstick on a first void urine (FVU) specimen or the presence of threads in a FVU specimen can be used to make a presumptive diagnosis of urethritis.

Investigations

• All men who have sex with men (MSM) should be tested for *N. gonorrhoeae* from any potentially exposed site and tested for *C. trachomatis* from FVU and anus. If a NAAT is positive for gonorrhoea, a culture should be performed before treatment.
• All heterosexual men assessed for STIs should be tested for *C. trachomatis* from a FVU specimen, regardless of symptoms and for *N. gonorrhoeae* if they have a urethritis.
• Consideration should be given to testing male patients with urethritis for *M. genitalium*, depending upon local availability and resources.

Management

• Recommended regimen for the index patient: doxycycline 100mg twice daily for seven days.
• Alternative regimens for the index patient: lymecycline 300mg bd for 10 days or tetracycline hydrochloride 500mg bd for 10 days
• If the index patient is, or is suspected to be *M. genitalium*-positive: azithromycin 500 mg stat, then 250 mg od for 4 days
• Recommended regimen for sexual contacts of nongonococcal nonchlamydial urethritis: doxycycline 100mg twice daily for seven days or azithromycin 500 mg stat, then 250 mg od for 4 days
• If the index patient was *M genitalium*-positive or considered at high risk and treated with azithromycin 500 mg stat then 250 mg od 4/7, the partner should also be treated with the same regimen.
• Follow up is only indicated if chlamydia is confirmed, if *M genitalium* is confirmed or if the man has persistent symptoms. A test of cure 4-5 weeks after treatment in those who tested positive for *M genitalium* should be performed.

**Persistent/Recurrent NGU**

• Consider testing for *Trichomonas vaginalis* if it is prevalent in the local population, using a NAAT and *M. genitalium* and *U. urealyticum* using a NAAT if available.
• Only treat if patient has definite symptoms of urethritis, or physical signs on examination AND microscopic evidence of urethritis.
• If doxycycline 100mg twice daily for seven days used as first line treatment, the, recommended regimen  is: azithromycin 500mg stat then 250mg for the next 4 days plus metronidazole 400 mg twice daily for 5 days, depending on local *T. vaginalis* prevalence.
• If azithromycin 500mg stat then 250mg for the next 4 days used as first line treatment, the recommend regimen is: moxifloxacin 400mg orally once daily for 7-14 days plus metronidazole 400mg twice daily for 5 days.

**Introduction**

Urethritis, or inflammation of the urethra, is a multifactorial condition which is sexually acquired in the majority of (but not all) cases. It is characterised by discharge, dysuria and/or urethral discomfort 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 void urine specimen (FVU) can also be used. Urethritis is described as either gonococcal, when *Neisseria gonorrhoeae* is detected, or nongonococcal (NGU) when it is not. The term nonspecific urethritis (NSU) applies to nongonococcal nonchlamydial urethritis and in order to prevent confusion should be avoided. It has been suggested that mucopurulent nongonococcal cervicitis is the female equivalent with approximately 20-40% of cases being due to infection with *Chlamydia trachomatis* and 5-20% *Mycoplasma genitalium*. (1-5)

There are a number of uncertainties with NGU. There is significant inter-observer and intraobserver error in performing and reading urethral slides and counting PMNLs, especially in samples with low grade inflammation. (6, 7) In many men with urethritis a known pathogen is not detected. (8-18)

**Aetiology**

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

The commonest organisms implicated are *C. trachomatis* and *M. genitalium*, with the latter perhaps causing more symptoms. (9, 10) Chlamydia and *M. genitalium* are more likely to be detected in:

- Younger patients with NGU, although this association is not as strong for *M genitalium*. (8, 10, 11)
- Those with a urethral discharge and/or dysuria. (5, 8, 11, 12)
- *M. genitalium* has been associated with balano-posthitis and *C. trachomatis* with a circinate balanitis. (19, 20)
  - The two organisms only infrequently coexist in the same individual with NGU (21), but dual infections have been identified in up to 10% of men in some studies. (8, 22)
  - Men with a urethral discharge have a higher bacterial load than those without. (23, 24)

In 30-80% of the cases with NGU neither *C. trachomatis* nor *M. genitalium* is detected. (8-17)

- Pathogen negative NGU is more likely with increasing age and the absence of discharge or clinical symptoms. (8, 11, 12)
• The isolation of *Trichomonas vaginalis* is dependent on the prevalence of the organism in the community. This infection appears to be uncommon in the United Kingdom and Western Europe although there are only limited studies using the new commercial NAAT tests for detecting *Trichomonas* which are more sensitive than previous tests.\(^{(25)}\) In the United States prevalences of 2.5-17% have been reported and this is associated with black race.\(^{(8, 11, 22, 25, 26)}\)
  - *T. vaginalis* isolation is greater in men >30 years \(^{(8, 26)}\) and may not always be associated with symptoms.\(^{(22, 25)}\)

• Ureaplasmas have been inconsistently associated with NGU.\(^{(16, 27)}\) Earlier studies did not differentiate between the two biovars *Ureaplasma urealyticum*, biovar 2 and *U. parvum* biovar 1. There is increasing evidence that it is only *U. urealyticum* biovar 2 which is pathogenic in some men but not *U. parvum*.\(^{(8, 28-31)}\) There is some evidence that the immune response may influence the development of NGU as in one study an association of *U. urealyticum* with NGU was only observed in men with fewer lifetime sex partners compared to those who had many.\(^{(29)}\)
  - *U. urealyticum* may account for 5-10% of cases of acute NGU.

• A urinary tract infection is uncommon in young men; one study found that it accounted for 6.4% (95% CI 1.5% 11.3%) of cases.\(^{(32)}\) If found, young men should be investigated for urinary abnormalities.

• Adenoviruses may account for perhaps 2-4% of symptomatic patients and this often associated with conjunctivitis.\(^{(13, 33)}\)

• Herpes simplex viruses types 1 and 2 are uncommon causes of NGU (2-3%) in the absence of typical genital ulceration.\(^{(13, 34)}\)

• *N. meningitidis, Haemophilus 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, whilst the role of Epstein Barr Virus is questionable.\(^{(35, 36)}\) There is emerging evidence that bacterial vaginosis-associated bacteria may be associated with NGU.\(^{(37, 38)}\)

• What causes organism negative NGU or idiopathic urethritis, as it is sometimes known, is unclear and has recently been reviewed by Horner.\(^{(39)}\) Some of these cases are almost certainly non-infective, but we do not currently have the tools to be able to differentiate probably non-infective from likely infective cases.\(^{(39)}\) Although the
evidence is weak the proportion due to either an unknown pathogenic sexually transmissible infection is likely to be low.(40)

Asymptomatic urethritis, without an observable discharge, probably has a different aetiology from symptomatic urethritis, with *C. trachomatis* and *M. genitalium* being detected less frequently.(9, 10, 12, 41) This guideline does not recommend testing asymptomatic men for non-gonococcal urethritis.

**Clinical features**

**SYMPTOMS**

- Urethral discharge
- Dysuria
- Penile tip irritation(10)
- Urethral discomfort and/or itch
- Nil

**SIGNS**

- Urethral discharge.
- Balano-posthitis(19)
- Normal examination

**COMPLICATIONS**

- Epididymo-orchitis
- Sexually acquired reactive arthritis / Reiter’s syndrome. These are infrequent with the prevalence being dependent on HLA B27 in the population.

**Diagnosis**

Symptomatic patients and those with a visible discharge should be assessed for the presence of urethritis. (IV, C)
The diagnosis of urethritis should be confirmed by demonstrating polymorphonuclear leucocytes (PMNLs) from the anterior urethra using a Gram stained or methylene-blue stained urethral smear, which should contain ≥5 PMNL per high power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs).(9, 42, 43)

- The quality of the smear is heavily dependent on how the smear is taken and there is both inter and intra-observer variation when interpreting the result.(6, 7)
- Either a 5 mm plastic loop or cotton tipped swab can be used, which should be introduced about 1 cm into the urethra. A 5 mm plastic loop is less painful than a Dacron swab, which is less painful than a Rayon swab.(44) Other methods are also used, including a sterile blunt curette or spatula.(45) (Ib, A)
- If a urethral discharge is present and can be adequately sampled without placing the loop or swab inside the meatus, this would be the recommended method for preparing a smear as it is likely to be preferred by the patient.(44) However, this has not been compared to the standard technique in a clinical trial. (IV, C)

Examining a stained preparation from a centrifuged sample of a first passed urine (FVU) specimen, containing ≥10 PMNL per high power (x1000) microscopic field (averaged over five fields with greatest concentration of PMNLs) is not possible in the majority of clinical laboratories, as centrifuges are not routinely available. Instead, a FVU specimen can be examined for threads and if present these can be stained and interpreted as for a spun deposit.(16, 46) (III, B)

**Management of symptomatic patients with a negative urethral smear.**

- Use a leucocyte esterase dipstick on the remains of the FVU specimen.
  - While positive leucocyte esterase activity on dipstick on an FVU specimen correlates with NGU and the detection of chlamydia(17, 47), it does not have adequate sensitivity to be considered a reliable rapid diagnostic test for acute NGU and false positives can occur.(48, 49)
  - It is therefore not recommended for diagnosis of NGU where microscopy is available. In the 2010 Centers for Disease Control and Prevention guideline a
leucocyte esterase dipstick $\geq 1+$ would be considered consistent with the presence of urethritis. (50) (IV, C) If both urethral smear and leucocyte esterase dipstick examination are normal, the patient can be reassured and advised to re-attend for an early morning smear if his symptoms do not settle. He should be advised to hold his urine overnight and to attend not having voided urine. It is good practice to advise the patient to take their last drink about 8 pm and to void about 3 hours later in order to help avoid waking with a full bladder. (IV, C)

• Empirical treatment without verifying the presence of urethritis is not recommended as there is a risk it may perpetuate their symptoms (IV). This treatment should only be given in exceptional circumstances. In such situations treatment of the partner(s) would also be indicated.

The sensitivity of the smear test for diagnosing urethritis, but probably not the FVU in detecting chlamydia (51, 52), 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. (IV, C)

Managing patients in settings in which microscopy is not available

Symptomatic patients should be referred to a centre which has microscopy available. However, some patients may not wish to re-attend another health care setting. This should be strongly discouraged as the sensitivity and specificity of other methods for diagnosing urethritis is imperfect compared to a urethral smear, in particular gonorrhoea may be missed. When microscopy is not available the following can be used to make a diagnosis of urethritis:

• The presence of a mucopurulent or purulent urethral discharge on examination
• $\geq 1+$ on a leucocyte esterase dipstick on an FVU specimen.(see above)
• The presence of threads in a FVU specimen. (53, 54) Threads may be physiological e.g. semen.
  (IV, C)

Investigations
• All men who have sex with men (MSM) should be tested for *N. gonorrhoeae* from any potentially exposed site including pharynx and rectum.(55) NAAT for *N. gonorrhoeae* has a much higher sensitivity than culture from pharynx and rectum.(56) If a NAAT is positive for gonorrhoea, a culture should be performed before treatment in order to document the resistance pattern.

• All MSM should be tested for *C. trachomatis* from FVU and anus.(55)

• All heterosexual men assessed for STIs should be tested for *C. trachomatis* from first void urine, regardless of symptoms.

• Heterosexual men should be tested for *N. gonorrhoeae* if they have a urethritis.

• If *N. gonorrhoeae* or *C. trachomatis* positive, management should be as specified in the European guidelines.

• Commercial testing for *M. genitalium* and *U. urealyticum* is not widely available in many countries.

• Testing male patients with urethritis for *M. genitalium* is likely to be helpful in the management of such cases and consideration should be given to testing for this organism depending upon local availability and resources.(57)

• In men with symptoms strongly suggestive of a UTI - for example, if the patient complains of severe dysuria, haematuria (microscopic or macroscopic), nocturia, urinary frequency, urgency, or is at low risk for a sexually transmitted infection a urinary dipstick analysis on a mid-stream urine specimen should be considered and the sample sent for culture and sensitivities.(32) Although a urinary dipstick is only 68-88% sensitive, it is inexpensive and a useful screening test.(32) If a urinary tract infection is confirmed consider further urological assessment. (IV, C)

**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 and correct use of condoms, including for oral sex, until he has completed therapy and his current partner(s) have been treated. (IV)
• Advice on safer sex (see UK national guideline on Safer Sex Advice 2012)
• The importance of complying with any follow-up arrangements made.

**Treatment**

In men with severe symptoms the 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*. In men with mild symptoms and microscopically proven low grade urethritis (5-15 PMNLs/hpf), another option is to review the patient after 3-7 days, preferably for an EMS, when the results of the NAAT(s) and gonorrhoea culture are available as sometimes urethritis can resolve without treatment.(58) If laboratory tests are positive, or he has persistent microscopic urethritis, appropriate antimicrobial treatment depending on which microorganism is detected can then be administered at the second visit.

Ideally, treatment should be effective (microbiological cure >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 not straightforward as persistence of inflammation may not indicate persistent infection.(16, 59, 60) It is important to note that detectable inflammation may persist for an unknown length of time, even when the putative organism has been eliminated.(61) Two recent large randomised controlled trials from the United States observed that both doxycycline and azithromycin are <85% in clinical cure.(18, 62)

**RECOMMENDED REGIMENS (GRADE OF RECOMMENDATION A)**

Doxycycline 100 mg twice a day orally for 7 days (Ib)

**ALTERNATIVE REGIMENS (A)**

Azithromycin 1 grm stat

Should not be used routinely because of the risk of inducing macrolide antimicrobial resistance with *M. genitalium*. (57)
Lymecycline 300mg bd for 10 days
Tetracycline hydrochloride 500mg bd for 10 days

If patient is, or suspected to be *M. genitalium*-positive
azithromycin 500 mg stat, then 250 mg od for 4 days (see above) (B, IIb)

**Doxycycline 100 mg bd for 7 days as first line therapy**
- Is probably > 95% effective in men who are chlamydia-positive. (18, 62, 63)
- Is effective also against rectal chlamydia of non-LGV type.
- Although only effective in < 50% on men who are *M. genitalium* positive there is no evidence it confers antimicrobial resistance and thus those who fail therapy should respond to a prolonged course of azithromycin. (see persistent NGU)
- It is as effective as azithromycin 1grm in men who are *U. urealyticum*-positive.

**Azithromycin 1 gram as first line therapy**
- Single dose therapy has the advantage of good adherence.
- Two recent well conducted RCTs demonstrated <90% efficacy in eradicating chlamydia and *M. genitalium*. (18, 62, 64)
  - There are a number of potential explanations for reduced efficacy in chlamydia-positive men with urethritis.(65, 66)
  - It has microbiological cure rates of 40–88% in men who are *M. genitalium*-positive, depending on background macrolide resistance in population.(57)
- *M. genitalium*-positive men who fail therapy are at risk of developing a 23sRNA gene mutations conferring antimicrobial. If this were to occur an extended 5 day azithromycin regimen would not be effective at eradicating the infection.(57, 67)
- It has been demonstrated to be ~80% effective in men who are *U. urealyticum*-positive.(31, 68)
- It has been demonstrated to be <80% effective in cure of rectal chlamydia.(69)

Lymecycline 300 mg bd for 10 days or tetracycline hydrochloride 500 mg bd for 10 days as first line therapy
- Are probably > 95% effective in men who are chlamydia-positive(70)
• Are < 50% effective in men who are *M. genitalium* positive

• Do not induce photosensitivity as doxycycline, and can be used in cases of sun exposure

• It is as effective as azithromycin 1 grm or doxycycline 100 mg bd for 7 days in men who are *U. urealyticum*-positive

**Azithromycin 500 mg stat then 250 mg od for 4 days as first line therapy**

• Although there this has not be assessed within a randomised controlled trial, there is reasonably good evidence that a prolonged course of azithromycin 500mg then 250mg daily for 4 days is more than 70-95% effective in eradicating *M. genitalium* depending on the background azithromycin resistance.(57)
  
  o It does not appear to induce macrolide antimicrobial resistance, although there are only limited reports in the literature evaluating this.(71)
  
  o A five day regimen is biologically more sensible than a single dose as it is a slow growing micro-organism.(57)

• A prolonged course of azithromycin may be biologically more effective than a single dose in eradicating *C. trachomatis* in men with urethritis.(66)

• There is an argument for using azithromycin 1 g then 250mg od 4 days as this regimen includes the recommended first line therapy azithromycin 1 g for chlamydia, however there is no evidence from clinical trials to support this statement .(57) (IV C)

**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. Partner(s) notification and management should be carried out with sensitivity, considering socio-cultural issues and avoiding stigma.

Current partner(s) should be tested and treated and the patient advised not to be sexually active until both have completed treatment.
If *C. trachomatis* or *N. gonorrhoeae* are detected it is important to ensure that all sexual partner(s) potentially at risk have been notified and managed as detailed in the European Chlamydia and Gonorrhoea guidelines. (available at http://www.iusti.org/regions/europe/euroguidelines.htm)

- 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 re-attend, he can be contacted and/or provider referral can be initiated for sexual contacts (IV, C).

In a study conducted before NAAT for *C. trachomatis* and *M. genitalium* was available there was no evidence of treatment benefit to partners of men with chlamydia-negative NGU.(72) There are, however, a number of issues which may influence decision making.

- *M. genitalium* accounts for approximately 15-30% of cases and there is a high concordance of infection in sexual partners.(73)
- *M. genitalium* probably causes disease in women and is a co-factor in HIV transmission.(5, 57, 74)
- There are reports of patients with persistent or recurrent *U. urealyticum*-positive urethritis being cured only after their sexual partner received appropriate treatment.(75)
- Doxycycline 100mg bd 7 days and azithromycin 1 g are sub-optimal treatments for *M. genitalium*. (see above)
- In the absence of randomised prospective studies and specific tests for *M. genitalium* it would seem sensible to treat partners of micro-organism-negative NGU, concurrently, to reduce risk of recurrent/persistent NGU in the index male and potentially reduce female morbidity with doxycycline 100 mg twice a day orally for 7 days or azithromycin 500 mgs then 250mgs od 4/7 (IV-C)
- If the index patient was *M genitalium*-positive or considered at high risk and treated with azithromycin 500 mgs then 250 mgs od 4/7 the partner should also be treated with the same regimen.(IV, C).

**Follow up for patients with NGU**

Follow up is only indicated if chlamydia is confirmed (see European guideline), if *M. genitalium* is confirmed or if the man has persistent symptoms. A test of cure 4-5 weeks after
treatment in those who tested positive for *M genitalium* should be performed(76). Patients who remain symptomatic should be asked to return to the clinic and retreated with appropriate regimen (see below) and the possibility of re-infection explored. (IV, C)

**Persistent and recurrent NGU**

Persistent NGU, when symptoms do not resolve following treatment, occurs in 15-25% of patients following initial treatment of acute NGU. Recurrent NGU is empirically defined as the recurrence of symptomatic urethritis occurring 30-90 days following treatment of acute NGU(16) and occurs in 10-20% of patients.(16, 77)

The aetiology of persistent NGU is probably multifactorial with an infectious agent being identified in <50% of cases.(11, 16, 67, 77) *M. genitalium* has been identified in 20-40%(11, 16, 67, 78) and *C. trachomatis* in 10%-20% in men treated with azithromycin 1grm.(62) *U. urealyticum* may also play a role in some men.(16, 31, 79) *Trichomonas vaginalis* can be identified in up to 10% in populations where it is endemic.(11) Herpes simplex virus should also be considered as this can cause dysuria without signs outside the urethra.

Any treatment of persistent NGU should cover *M. genitalium* and *T. vaginalis*. The only randomised controlled trial for persistent NGU was undertaken before *M. genitalium* had been identified as an important pathogen and used erythromycin, an older generation macrolide.(80) Although a 3 week course was better than placebo it is not clear how relevant this regimen is today given that better macrolides are available with less side effects.(81)

As there is no evidence that female partners of men with persistent/recurrent NGU are at increased risk of pelvic inflammatory disease, the historical advice has been that they do not need to be retreated if treated appropriately at first. However, in view of the emerging evidence that persistence of *M. genitalium* post single dose azithromycin 1g is probably equally likely in men and women and doxycycline is < 50% effective (82), it is likely that re-treatment of the sexual partner and index case will be beneficial if persistent/recurrent NGU in the index case resolves following extended therapy but subsequently recurs. This remains
an area where further research is needed. It would be sensible to use the extended regimen demonstrated to be effective unless contraindicated. (IV, C)

DIAGNOSIS OF PERSISTENT/RECURRENT NGU (IV, C)

- Only undertake a Gram or methylene blue stained urethral smear in men who are symptomatic
- For those patients with confirmed chlamydia at initial presentation please refer to European Chlamydia guideline for further guidance on repeat NAAT testing.
- Consider testing for *Trichomonas vaginalis* if it is prevalent in the local population using a NAAT if available.
- Consider testing for *M. genitalium* and *U. urealyticum* if available.

MANAGEMENT OF PERSISTENT/RECURRENT NGU (IV, C)

- 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 AND microscopic evidence of urethritis.
- Reassure asymptomatic patients that no further test or treatment is necessary.

RECOMMENDED REGIMENS – second attendance or first follow-up visit

Patient symptomatic or an observable discharge present AND microscopic evidence of urethritis. (5, 16, 60, 71, 83)

**Preferred regimens**

**Doxycycline 100 mg bd 7 days prescribed as first line therapy**

Azithromycin 500 mg stat then 250mg for the next 4 days (III, B) plus metronidazole 400 mg twice daily for 5 days depending on local *T. vaginalis* prevalence (IV, C)
**Azithromycin 500mgs stat then 250mgs od 4 days prescribed first line therapy**

Moxifloxacin 400 mg orally once daily for 7-14 days (IIIb, B)  
plus metronidazole 400 mg twice daily for 5 days (IV, C)

NB: moxifloxacin should be used with caution and reserved for treatment failures  
which are thought secondary to macrolide resistant *M. genitalium*, because of rare but  
serious adverse hepatic reactions. One recent study suggests a 14 day course is more  
effective than a seven day course if *M. genitalium* is involved, although a 7 day  
course has proven effective in Norway.(57, 71, 84)

**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.

- Moxifloxacin 400mg orally once daily for 7-14 days (IIIb, B)
- Urological investigation is usually normal unless the patient has urinary flow  
  problems (85, 86) and is not recommended. (IV, C)
- Chronic abacterial prostatitis and the chronic pelvic pain syndrome and psychosexual  
  causes should be considered in the differential diagnosis.(80, 87, 88)
- For men with persistent or recurrent urethritis, there is currently no evidence that  
  retreatment of an appropriately treated sexual partner is beneficial (see above).However, it would be prudent to retreat the partner if the man with chronic  
  NGU is cured following extended therapy but subsequently recurs on sexual  
  intercourse. (IV, C) In this scenario the index case should be retreated and the sexual  
  partner, if female, should be examined and tested for *Trichomonas vaginalis* and  
  bacterial vaginosis regardless of symptoms. All sexual partners should be treated  
  concurrently with the same antibiotic regimen which was effective in the index.
- Erythromycin 500 mg four times daily for 3 weeks has been shown to be effective(80)  
  but this was undertaken before the new macrolides were generally available.(81)  
  Clarithromycin is better absorbed, has an improved side effect profile and can be
taken twice a day. Consideration should be given to using Clarithromycin 500mgs twice daily for 3/52 as an alternative to erythromycin and is recommended in patients who are *U. urealyticum* positive.(88)(IV, C)

- Horner and colleagues recently published a “How to article” detailing how to manage men attending a sexual health clinic with persistent symptoms with or without urethritis.(86, 88) This describes a structured biopsychosocial, holistic management strategy incorporating evidence based pharmacotherapy for men who have the chronic pelvic pain syndrome (CPPS) a complex condition which overlaps with chronic urethritis.

**Auditable Outcome Measures**

- All patients with NGU should be screened for genital infection with *C. trachomatis*.
- All patients identified with NGU should have partner notification carried out according to the published standards of the IUSTI;
- All patients identified with NGU should be offered written information about STIs and their prevention;
- All patients with NGU should receive first-line treatment or the reasons for not doing so documented.
- Only undertake a Gram or methylene blue stained urethral smear in men who are symptomatic

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

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Prevalence</th>
<th>Reference</th>
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<tbody>
<tr>
<td><em>C. trachomatis</em></td>
<td>11-50%</td>
<td>(8, 9, 11, 13, 15-18, 22, 29, 62, 89-95)</td>
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<tr>
<td><em>M. genitalium</em></td>
<td>6-50%</td>
<td>(8-11, 13, 16, 18, 19, 22, 29, 62, 91, 93-96)</td>
</tr>
<tr>
<td><em>Ureaplasma urealyticum</em></td>
<td>11-26%</td>
<td>(8, 16, 18, 29, 93, 95, 97, 98)</td>
</tr>
<tr>
<td><em>T. vaginalis</em></td>
<td>1-20%</td>
<td>(8, 11, 22, 25, 62, 99)</td>
</tr>
<tr>
<td>Adenoviruses</td>
<td>2-4%</td>
<td>(13, 33)</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Herpes simplex virus</td>
<td>2-3%</td>
<td>(13, 34)</td>
</tr>
</tbody>
</table>

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**List of contributing organisations**
This guideline has been produced on behalf of the following organisations:
The European Branch of the International Union against Sexually Transmitted Infections (IUSTI Europe)
The European Academy of Dermatology and Venereology (EADV)
The European Dermatology Forum (EDF)
The European Society of Clinical Microbiology and Infectious Diseases (ESCMID);
The Union of European Medical Specialists (UEMS)
The European Centre for Disease Prevention and Control (ECDC) and the European Office of the World Health Organisation (WHO-Europe) also contributed to its development.

References


APPENDICES

Levels of Evidence
Ia. Evidence obtained from metaanalysis 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 over all 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.

Declarations of Interest
Patrick J. Horner: - Has received funding from Cepheid directly and indirectly for lecturing on point of care testing and undertaking research on the cost effectiveness of their CT/NG assay. Has also received payment from Atlas Genetics for an article in the Parliamentary Review on the benefits of point of care technology in improving the cost effectiveness of sexual health services. Has also received an honorarium from Hologic for an education talk on STI diagnostics and funding for providing expert advice on M. genitalium diagnostics.
Karla Blee – none to declare
Willem van der Meijden – none to declare
Lars Falk – none to declare
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