Nongonococcal urethritis
management in general practice

Nongonococcal urethritis (NGU) is a common sexually transmitted infection in men. Despite significant advances in the understanding of the aetiology and treatment of this disease over the last decade, it can still be difficult to diagnose and manage.

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Ancient Greek and Roman medical writers originally described urethritis as the persistent flow of semen in the absence of sexual desire. Feelings of weakness and exhaustion were ascribed to the debilitating effects of the loss of semen, 'the principle of life', such that the patient was eventually consumed by wasting.[1] These original descriptions were probably referring to gonococcal urethritis. It is now understood that urethritis is either gonococcal or nongonococcal, and is the result of inflammation of the urethra. Female partners of men with symptomatic or asymptomatic urethritis may present with pelvic inflammatory disease, which adds to the public health implications of this disease.

Is it urethritis?

Typically, urethritis is a disease of young, sexually active men that can be acquired by vaginal, anal or oral sex. Its incidence peaks in men aged 20 to 24 years,[2] and increases with the number of sexual partners. The typical symptoms are urethral discharge, dysuria, and meatal irritation or itch; however, it has been estimated that 5 to 58% of patients are asymptomatic.[3]

Clinically, it is impossible to distinguish absolutely gonococcal from nongonococcal urethritis (NGU). The discharge in patients with gonorrhoea is thought to be more purulent and have a more abrupt onset than in those with NGU, but this is not reliable. Gonorrhoea usually develops two to six days after exposure to *Neisseria gonorrhoeae*, whereas NGU develops one to five weeks after exposure to the causative organism.[2]

Taking a detailed sexual history, focusing on recent past sexual contacts, may provide the doctor with clues to the aetiology of the infection. Symptoms, such as urgency and frequency, are not usually associated with NGU. If these symptoms are present, urinary tract infection should be excluded.

As many patients with NGU may be minimally symptomatic or asymptomatic they may not be aware that they have the disease. Such patients may present with Reiter's syndrome or epididymitis[4] or as contacts of women who are infected with *Chlamydia trachomatis* or have pelvic inflammatory disease.

IN SUMMARY

- **Nongonococcal urethritis (NGU) is one of the most common sexually transmitted diseases (STDs) in young men; it is often asymptomatic.**
- **Clinically it is impossible to differentiate *Neisseria gonorrhoeae* infection from *Chlamydia trachomatis* infection; all patients with suspected urethritis need formal testing for these organisms.**
- **Most cases of NGU are not due to *C. trachomatis*.**
- **All patients with NGU should be offered testing for other STDs.**
- **For patients with uncomplicated *C. trachomatis* urethritis, azithromycin 1 g in a single dose is as effective as doxycycline 100 mg given twice daily for 7 to 10 days.**

AUSTRAL INTERNATIONAL

Chlamydia trachomatis

What causes nongonococcal urethritis?

Although it is commonly believed that most cases of NGU are caused by *C. trachomatis* or *Ureaplasma urealyticum*, up to 50% of cases have other causes (see the box opposite).[3]

C. trachomatis is pathogenic in all men. Treatment of *C. trachomatis* infection results in eradication of the organism unless there is coinfection with another organism or the patient has become reinfected since treatment. The role of *U. urealyticum* in NGU is less clear as the organism is a common commensal of the genital tract; however, it is found in greater numbers in men with NGU than in those without.[5]

Nonchlamydial NGU has been associated independently with both the number of sexual partners and the inconsistent use of condoms. Fellatio in homosexual men is an independent risk factor for the development of NGU, suggesting a role for oral factors as a potential aetiological source.[6] This association has not been confirmed in heterosexual men because of the rarity of insertive oral sex being the patients' sole sexual exposure.[7] Oral pathogens, such as *Neisseria meningitidis, Haemophilus parainfluenzae* and *Haemophilus influenzae*, have been implicated in NGU, although they are less common.[2,4]

Aetiology of nongonococcal urethritis

Common causes

- *Chlamydia trachomatis* (responsible for 19–31% of cases; symptomatic urethritis)[3]
- *Ureaplasma urealyticum* (9–42%)[3]
- *Mycoplasma genitalium* (15–25%)[3]
- *Trichomonas vaginalis* (1–12%, depending on geographic prevalence)[3]
- *Neisseria meningitidis, Haemophilus influenzae, Haemophilus parainfluenzae* (1–2%)
- Herpes simplex virus (<2%)[2]

Less common associations

- Adenovirus
- Candida
- Coliforms
- Drugs (e.g. after using isotretinoin for acne)
- Posturological procedure
- Wegener's granulomatosis
- Reiter's syndrome

Undetermined role

- *Gardnerella vaginalis*
- *Mycoplasma hominus*
- Group B streptococcus

Figure 1. Meatal inflammation and urethral discharge.

Clinical evaluation of men with suspected urethritis

Take a history, looking for:

- Urethral discharge
- Dysuria
- Sticky urethral meatus

Examine the patient (supine) for:

- Discharge
- Meatal inflammation

Exclude the following:

- Epididymitis: are the testes tender on palpation?
- Prostatitis: is there pain on ejaculation, pain between the anus and scrotum, tender prostate on palpatation, or penile tip pain?
- Balanitis: are there patches of erythema, or is there an itch or white discharge?
- Urinary tract infection: are there symptoms of frequency and urgency?

Take the following samples:

- Swab of discharge, by milking the urethra, for Gram stain smear and trans-swab for *Neisseria gonorrhoeae*
- First catch urine specimen for chlamydia polymerase chain reaction
- Others according to sexual history – e.g. anal and pharyngeal swabs to test for *Chlamydia trachomatis* and *N. gonorrhoeae*, blood samples for HIV, hepatitis B and C, and syphilis serology

With the development of more sensitive tests, the protozoan *Trichomonas vaginalis* is now thought to have a greater role in NGU.[3] It is more likely to be an important pathogen in cases of NGU in geographical areas of high prevalence, such as in rural and remote regions of Australia. Treatment targeted at *T. vaginalis* is usually reserved for patients who do not respond to first line therapy.

Herpes simplex is responsible for 2% of urethritis cases; such patients usually have genital skin lesions.[2]

Infection with *Candida albicans* usually presents with balanitis in men rather than urethritis.

Bacterial urethritis may occur in association with a urethral stricture, prostatitis, or posturological invasive procedure.[2]

In 35% of cases of NGU there is no identifiable pathogen.[5] NGU can be caused by noninfectious, nonsexually transmitted agents that irritate the urethral mucosa.

How is it investigated?

Examination

With the patient lying supine inspect the penis, scrotal sac, and surrounding skin. Examine the urethral meatus, retracting the foreskin in uncircumcised men. Visual inspection or 'milking' the urethra may reveal evidence of meatal inflammation and a purulent discharge (Figure 1). Finally, palpate the testes and epididymis to exclude epididymitis (see the box opposite).

Microscopy

Obtain a smear of the urethral discharge for Gram staining. This is straightforward in symptomatic men and involves taking a sample of the discharge from the tip of the penis and rolling it on a slide. Gram staining facilities are not often available in general practice; in this case air dry the specimen and send it to the laboratory for reporting. NGU is defined microscopically by the presence of more than 5 to 10 polymorphonuclear leucocytes per high power field in the absence of Gram negative intracellular diplococci (Figure 2).

In practice, simple macroscopic examination of the first catch urine may reveal 'threads' or strands of polymorphonuclear leucocytes in the urine, suggesting anterior urethritis (Figure 3). The presence of threads alone should not, however, be used to diagnose urethritis.[8] Threads are less common in NGU than in gonococcal urethritis.[8]

Testing for C. trachomatis and N. gonorrhoeae

Men presenting with a urethral discharge should always be tested for *C. trachomatis* and *N. gonorrhoeae* infections. Depending on local prevalence, the infections may coexist in up to 30% of cases.[2]

DNA amplification techniques, such as polymerase chain reaction (PCR) and ligase chain reaction (LCR), detect small amounts of *C. trachomatis* in the first catch urine specimen. These noninvasive tests have replaced the older methods of diagnosis, and there is no need to subject men to painful urethral swabbing. PCR and LCR are equally effective and have superior sensitivity and specificity (in both asymptomatic and symptomatic men) to urethral swabbing.

To test for *N. gonorrhoeae* infection place a swab of the urethral discharge in simple trans-swab medium for culture by the laboratory. The swabbing of multiple sites, including the rectum and throat, is recommended in men who have sex with men.

Other microbiological tests

If requested on the initial specimen some laboratories will culture for *U. urealyticum* and other bacterial pathogens, such as *H. influenzae*, *H. parainfluenzae* and *N. meningitidis*, on the urethral swab.

T. vaginalis can be identified by wet mount examination (that is, examination of the specimen in a drop of normal saline at x40 magnification) or by culturing on Diamond's medium. Commercial DNA amplification tests for the detection of *T.*

vaginalis and other organisms, such as *Mycoplasma genitalium*, are not yet available. DNA amplification tests for the detection of *T. vaginalis* and *M. genitalium* have been developed but are not yet available for commercial use.

Tests for other STDs

To assist in the effective management and prevention of other sexually transmitted diseases (STDs), all patients and their contacts should be offered screening tests for STDs such as HIV infection, hepatitis B and syphilis.

How are patients treated?

Despite the development of improved diagnostic tests and a greater understanding of the spectrum of organisms causing NGU, symptomatic patients are usually prescribed empirical treatment at the initial visit, before a specific bacteriological cause has been confirmed.

The long acting macrolide antibiotic azithromycin (Zithromax), given as a single 1 g dose, is as effective as seven days' doxycycline treatment (100 mg twice daily) for patients with chlamydial NGU. In addition, it improves compliance and thus leads to fewer patients infected with *C. trachomatis* who are partially treated.[9] Although currently azithromycin is indicated only for uncomplicated *C. trachomatis* infection, its spectrum of activity should provide good antibiotic cover for many other organisms associated with NGU. It is more expensive than doxycycline; however, cost–benefit analysis has demonstrated an overall cost saving to the health care system because of prevention of long term sequelae.[9]

Several other effective regimens are recommended in Australia for the treatment of patients with NGU that is not caused by *C. trachomatis* (see the box opposite).

Antibiotic treatment is associated with potential side effects. For example, azithromycin may cause mild nausea and diarrhoea, and doxycycline, although generally well tolerated, can cause a photoallergic rash, urticaria and exacerbation of systemic lupus erythematosis. Doxycycline can also lead to gastrointestinal upset and has been shown to interact with the oral contraceptive pill.[10]

Should sexual contacts be treated?

Partners of patients with NGU should be contacted, tested for *C. trachomatis* infection and treated. A recent study recommended that patients should refer partners with whom they had had sexual contact within 30 days of the onset of symptoms or within 60 days if they were asymptomatic.[11] The Commonwealth Government's guidelines recommend that for patients with asymptomatic infections, partners in the previous six months be contacted.[12]

Follow up of contacts is essential as long term sequelae of *C. trachomatis* infection in women include salpingitis

Drug therapy for nongonococcal urethritis

Recommended regimen

Azithromycin (Zithromax) 1 g orally as a single dose* or

Doxycycline 100 mg orally twice daily for 7–10 days

Alternative regimen

Erythromycin stearate (Erythrocin Oral) 500 mg orally three times daily for 7–10 days

Resistant and/or persistent NGU

Metronidazole (Flagyl, Metrogyl, Metronide) 2 g as a single dose and/or erythromycin 500 mg orally for 10–12 days

*In Australia approved only for uncomplicated *C. trachomatis* infection.

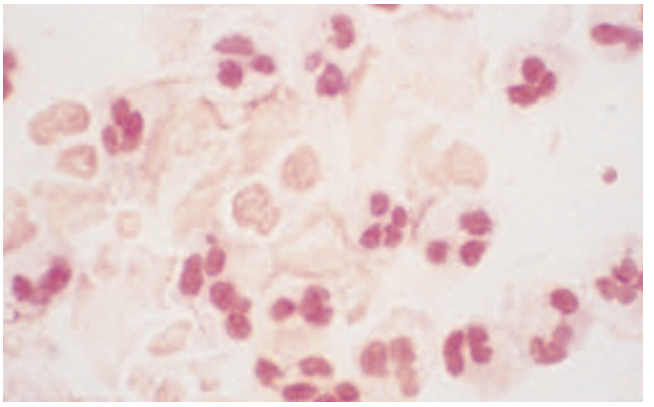

Figure 2. Gram stain of urethral discharge (x100 magnification). Nongonococcal urethritis is defined microscopically by the presence of greater than 5 to 10 polymorphonuclear leucocytes per high power field. Note the absence of intracellular Gram negative diplococci.

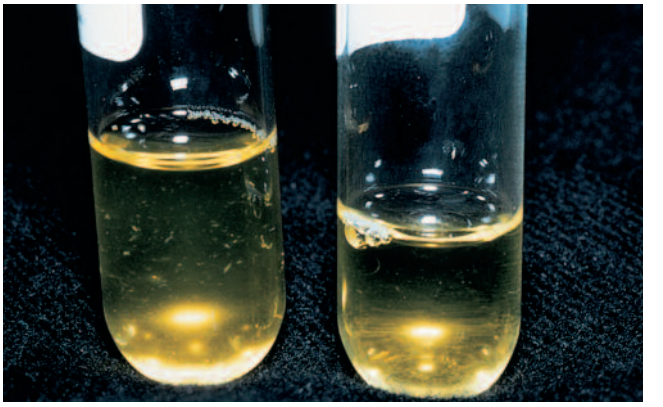

Figure 3. Two glasses of urine. The glass on the left is the first catch urine with threads or strands of polymorphonuclear leucocytes visible in the urine. The glass on the right is the midstream urine, which has no threads visible. The presence of threads in the first catch urine is suggestive of anterior urethritis.

MedicineToday **PATIENT HANDOUT**

Nongonococcal urethritis: what you need to know

What is nongonococcal urethritis?

Nongonococcal urethritis (NGU) is a common sexually transmitted infection in men. It is often caused by *Chlamydia trachomatis* but can also be due to contact with normal vaginal or throat bugs.

What are the symptoms?

A discharge from the tip of the penis or pain when urinating can be symptoms of urethritis. Sometimes you can have the infection with no symptoms at all.

How does someone get infected?

Infection is transmitted by unprotected vaginal, anal or oral sex.

What tests need to be done?

The doctor will ask for a urine sample and a specimen of discharge from the tip of the penis. For the best results do not pass urine for three hours before the test.

The doctor may also suggest you have a blood test to screen for HIV, hepatitis and syphilis.

Can it be treated?

NGU caused by the bug *Chlamydia* is usually cured by taking a single daily dose of an antibiotic called azithromycin (Zithromax). You should expect your symptoms to clear up within 48 hours of taking this medication.

You may instead be given an antibiotic called doxycycline. Some people taking this antibiotic develop a skin rash if they go out in the sun; sun protection is needed to stop this happening.

In rare cases, the antibiotic given to you may cause diarrhoea and it may make you feel sick.

Should my partner be treated?

Yes, all partners with whom you have had sexual contact in the last few months need to be seen by a doctor for some tests and treatment. It is common for a person to be infected without knowing that anything is wrong. Women infected with *Chlamydia* who are not treated may become infertile. This is one of the reasons why it is important to try as hard as possible to contact your partners.

Can it come back?

Yes, symptoms of NGU can return. This may be because you are infected with a bug other than *Chlamydia* or you are infected with a bug that does not respond to the original treatment. You may also be reinfected by a partner who has not been treated.

What are the complications of infection?

In men with NGU a structure surrounding the testis (inside the scrotum) called the epididymis may become inflamed, or swollen. Long term testicular discomfort and urethral irritation may also occur.

In men infertility is rare after NGU, even in those who have had recurrent problems with infections.

What else do I need to know?

- You should not have sex until you and your partner have been treated.
- Proper use of condoms (from the beginning of insertion to the end of intercourse) helps prevent you from getting NGU.
- Return to your doctor for a check up one week after treatment.
- Persistent or recurrent NGU does not mean you have AIDS or cancer.
- One episode of NGU does not protect you from further episodes of the disease.

and tubal infertility. Abstinence from intercourse is advised until patients and their partners have been treated and symptoms resolved (see the patient handout above).

Patients can be given contact letters (see the box on page 36) to assist in anonymous contact tracing. Alternatively they can be referred to a sexual health service that provides trained counsellors for this purpose.

Are there any complications?

NGU is often self-limiting in patients who are not treated. Epididymitis or conjunctivitis complicates 1 to 2% of cases.[2] The effectiveness of azithromycin to treat complicated infection has not yet been determined, and management should proceed along standard lines – that is, 10 to 15 days' treatment with erythromycin. The frequency of Reiter's syndrome (diagnosed by the classic triad of urethritis, conjunctivitis and arthro - pathy) that develops as a consequence of NGU is unknown.

How should patients be followed up?

Patients should be reviewed one week after treatment to assess:

- resolution of symptoms
- compliance
- risk of reinfection
- contact tracing and partner notification.

If the patient has complied with treatment and is asymptomatic, further testing is not required. The follow up consultation also provides an opportunity to discuss safer sex practices and testing for other STDs.

What if there is a recurrence?

If there is a recurrence of NGU after treatment consider poor compliance, re-exposure to an untreated partner, or reinfection by a new partner. If these factors are excluded, repeat testing may be indicated; however, be aware that *C. trachomatis* PCR can remain positive for

Example of a contact letter

Dear _____

You have come into contact with a person who has been diagnosed with nongonococcal urethritis (NGU). He has received a course of _____.

Please see your doctor so that you can be assessed for the presence of a sexually transmitted disease. The doctor will carry out the appropriate tests, including swabs and cultures (e.g. for chlamydia infection and gonorrhoea).

Many people who come into contact with NGU have no symptoms and may have negative test results. Contacts can be carriers of *Chlamydia trachomatis*. For this reason you may need treatment despite test result findings.

Thank you.

Medical Officer

up to three weeks after treatment.[3]

T. vaginalis may cause persistent urethritis; this can be managed effectively with a single 2 g dose of metronidazole (Flagyl, Metrogyl, Metronide). Another cause of persistent urethritis may be a strain of *U. urealyticum* that is resistant to doxycycline. In this case patients should respond to a course of erythromycin for 7 to 10 days.[2]

Some men present with symptoms of persistent urethritis but have no objective evidence of the disease. Referral of these patients to a sexual health service, if available in your area, may be helpful. Psychological factors, such as unresolved guilt, may create a feeling of urethral 'awareness' for which reassurance should be given and counselling offered. Should symptoms persist and become troublesome, the advice of an urologist may be needed.[2]

Research into the immunological mechanisms of NGU may provide more information on the aetiology of recurrent and true persistent urethritis.

Conclusion

NGU is a common, often asymptomatic, STD affecting sexually active men. The precise understanding of the aetiology of this disease is limited by the lack of availability of diagnostic tests; however, *C. trachomatis* and *U. urealyticum* are often implicated. Due to serious long term sequelae of *C. trachomatis* infection in women, contact tracing and partner notification are important to help prevent complications and spread of NGU. MT

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