

Non-specific urethritis and mycoplasma genitalium

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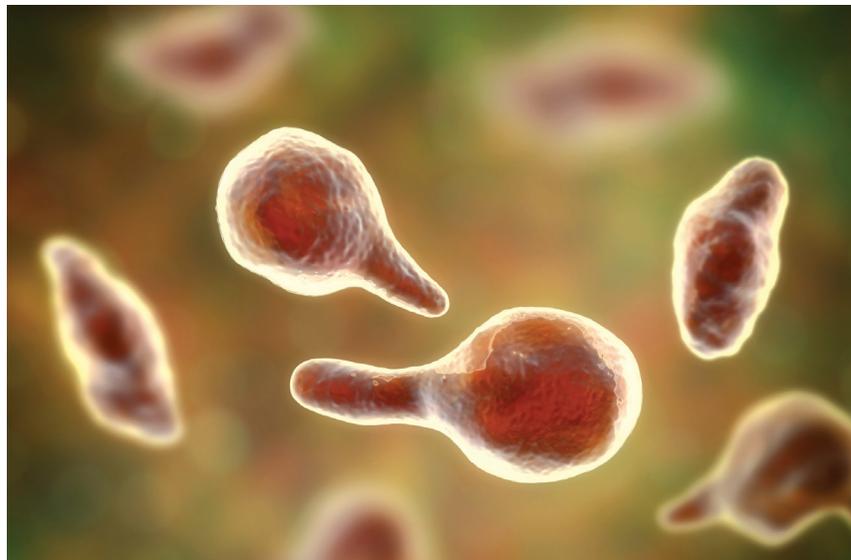
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***Mycoplasma genitalium* is a little known, yet common, sexually transmitted pathogen. Its increasing resistance to first- and second-line antibiotics and declining cure rates are cause for concern, which means testing for the organism in symptomatic men with non-specific urethritis is important.**

In January 2019, the National Institute for Health and Care Excellence (NICE) published a Clinical Knowledge Summary on the investigation and management of male urethritis.¹ The article recommends that all men presenting with symptoms of urethritis should be referred to a genitourinary medicine or specialist sexual health centre, as the best placed services for sexually transmitted infection (STI) screening, contact tracing and partner notification.¹

The document also gives guidance on how to manage these men in primary care when referral is not possible or declined. However, a £700 million real-terms reduction in public health spending since 2014, which directly funds sexual health services in England, has led to a significant restriction in access to these services.² Without renewed investment in community sexual health services, general practitioners and those with an interest in men's health are likely to be managing more of this condition.

'Urethritis' is a term that describes inflammation of the urethra. In men,



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Mycoplasma genitalium bacteria, illustration. *Mycoplasma genitalium* is a sexually transmitted organism that remains little known among the general public and wider medical community. Its prevalence and antibiotic resistance is a cause for concern

urethritis can present with a burning or stinging pain on urination, and mucopurulent or purulent penile discharge. The cause of urethritis is most often an STI; however, there are also non-infectious causes such as irritation from soaps or spermicides, trauma from vigorous sex, masturbation or catheterisation. Infectious cases of urethritis can be passed to female partners resulting in pelvic inflammatory disease, which can lead to subfertility if left untreated.

Causative organisms

Urethritis is commonly classified as either 'gonococcal' meaning that it is caused by the organism *Neisseria gonorrhoea*, or 'non-gonococcal', which is used interchangeably with

the term 'non-specific urethritis' (NSU). According to the British Association for Sexual Health and HIV (BASHH) the commonest causative organism of non-specific urethritis is *Chlamydia trachomatis*, accounting for 11–50% of cases. The less well known *Mycoplasma genitalium* accounts for the second most significant proportion of NSU cases at 10–20%.³ Other culprits include ureaplasma, *Trichomonas vaginalis*, adenovirus and *Herpes simplex virus*.

Mycoplasma genitalium

Mycoplasma genitalium is only recently understood to be a significant sexually transmitted pathogen. While it has been the focus of much research and discussion in the genitourinary medicine arena in recent years, very

little is known about it in the wider medical community and among the general public.

Mycoplasma genitalium is a fastidious organism that is difficult to culture. The development of nucleic acid amplification testing (NAAT) has made testing possible; however, large-scale commercial testing platforms have only recently become available. Newer commercial assays also have the ability to test positive samples for macrolide antibiotic resistance.

Diagnosis

Diagnosing urethritis and identifying the infectious organism will depend on the clinical setting. In genitourinary medicine and specialist sexual health centres, penile urethral swabs allow for immediate Gram staining and microscopy. The presence of leucocytes above a threshold value indicates inflammation, and thus is

diagnostic for urethritis. Where this facility is not available, the alternative is a leukocyte positive first-void urine sample, or the presence of urinary threads (strands of mucus or pus) on inspection of the sample. However, this approach is not as sensitive or specific as microscopy of a urethral swab, which is one reason why referral to specialist centres is recommended for all men.¹

Another advantage of microscopy of urethral swabs is the ability to detect intracellular Gram-negative diplococci, diagnostic for *Neisseria gonorrhoea*. Culture and sensitivity testing of such samples can then be sent prior to starting treatment, which is essential in the evolving landscape of multidrug resistant *Neisseria gonorrhoea*.

NAAT of first-pass urine sample is an alternative way to diagnose *Neisseria gonorrhoea* and is the standard of care in diagnosing *Chlamydia trachomatis*. Highly sensitive and specific, a single

sample is sufficient to test for both organisms and forms the basis of routine asymptomatic STI screening. However, if positive, it provides no information on antibiotic sensitivity. If *Neisseria gonorrhoea* is suspected or confirmed, then urethral swabs for culture and sensitivity testing should also be performed.⁴

In December 2018, BASHH published guidelines recommending testing all men with NSU for *Mycoplasma genitalium*.³ However, it was recognised by NICE that testing varies according to local availability.¹ A freedom of information request from BASHH to 125 public health commissioners revealed that only 1 in 10 were planning to make funding available for *Mycoplasma genitalium* testing in their 2019–20 budgets.⁵ Where there is no local provision for *Mycoplasma genitalium* testing, samples can be sent to the Public Health England Reference Laboratory.

	<i>Neisseria gonorrhoea</i>	<i>Chlamydia trachomatis</i>	<i>Mycoplasma genitalium</i>
Diagnosis	Urethral swab for microscopy, culture and sensitivity, and nucleic acid amplification (NAAT) testing of first-pass urine	NAAT of first-pass urine	NAAT of first-pass urine + test for macrolide resistance, where available
First-line treatment recommendation for uncomplicated infection	If antibiotic susceptibility unknown use ceftriaxone 1g intramuscularly as a single dose	Doxycycline 100mg, twice daily for 7 days	Doxycycline 100mg, twice daily for 7 days; followed by azithromycin 1g orally as a single dose, then 500mg once daily for 2 days
Preventing re-infection	Abstain from sexual activity until 7 days after both patient and partner(s) complete treatment	Abstain from sexual activity until both patient and partner(s) complete 7-day course of doxycycline	Abstain from sexual activity for 14 days from start of treatment for both patient and partner(s), and until resolution of symptoms
Partner notification	All partners within the preceding 2 weeks (or the last partner if longer than 2 weeks ago)	All contacts since, and in the 4 weeks prior to, the onset of symptoms	Only current partner(s) should be tested and treated if positive
Follow-up	Test of cure 7 days following treatment (for RNA amplification testing) or 14 days following treatment (for DNA amplification testing). Positive samples should be followed by culture	Check for resolution of symptoms after 1–2 weeks. Routine test of cure not recommended	Test of cure 5 weeks post-treatment

Table 1. Key points for the diagnosis and management of common infective causes of male urethritis^{1,3,4,8}

Antibiotic resistance

But why is testing for *Mycoplasma genitalium* so important? The answer is the concerning increase in its resistance to both first- and second-line antibiotic regimens and declining cure rates.⁶

Patients with NSU have historically been empirically treated for chlamydia with a single dose of the macrolide azithromycin and no test of cure. For those who were actually infected with *Mycoplasma genitalium*, this incompletely treats their infection, induces resistance, and allows the resistant strain to be passed on to future sexual contacts. There is therefore alarm in the sexual health community that without the widespread introduction of testing for *Mycoplasma genitalium*, it could well become a 'superbug' within a decade, without any effective treatment.⁵ BASHH has subsequently changed their first-line treatment recommendation for chlamydia in an attempt to limit the emergence of macrolide-resistant *Mycoplasma genitalium*.⁷

Management

Firstly, it is important to remember that prevention is better than cure. Public health education regarding safe sexual practice with condoms, and minimising the number of sexual partners, plays a vital role in preventing spread of disease. Access to sexual health screening should be readily available, and for men presenting with symptoms of urethritis, opportunistic testing for HIV and syphilis should also be performed.

NICE advocate referring all men with suspected urethritis to genitourinary clinics as the best-placed service for diagnosis, treatment and guidance through partner tracing and notification.¹ Follow up to ensure resolution of symptoms and test of cure following treatment should be performed in all men diagnosed with *Neisseria gonorrhoea* and *Mycoplasma genitalium* due to the propensity of these organisms to develop antibiotic resistance. A summary of the NICE and BASHH guidelines for the diagnosis and management of the three most common NSU-causing organisms is available in Table 1.

Conclusion

The emergence of *Mycoplasma genitalium* as a common sexually transmitted pathogen and its propensity to develop antibiotic resistance highlights the importance of appropriate diagnostics, treatment and follow-up for men presenting with symptoms of urethritis. Those with an interest in men's health should be aware of new NICE Clinical Knowledge Summary for the management of this condition.

Declaration of interests: none declared.

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