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Mycoplasma genitalium Infection in Men

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Abstract

M. genitalium is one of the major causes of non-gonococcal urethritis (NGU) worldwide but an uncommon sexually transmitted infection (STI) in the general population. The risk of sexual transmission is probably lower than for *C. trachomatis*. Infection in men is usually asymptomatic and it is likely most men resolve infection without developing disease. The incubation period for NGU caused by *M. genitalium* is probably longer than for NGU caused by *C. trachomatis*. The clinical characteristics of symptomatic NGU have not been shown to identify the pathogen specific aetiology. Effective treatment of men and their sexual partner(s) is complicated as macrolide antimicrobial resistance is now common in many countries, conceivably due to the widespread use of azithromycin 1g to treat STIs and the limited availability of diagnostic tests for *M. genitalium*. Improved outcomes in men with NGU and better antimicrobial stewardship are likely to arise from the introduction of diagnostic *M. genitalium* NAAT testing including antimicrobial resistance testing in men with symptoms of NGU as well as in their current sexual partner(s). The cost effectiveness of these approaches need further evaluation. The evidence that *M. genitalium* causes epididymo-orchitis, proctitis, reactive arthritis and facilitates HIV transmission in men is weak, although biological plausible. In the absence of randomised controlled trials demonstrating cost effectiveness, screening asymptomatic men cannot be recommended.

Introduction

Mycoplasma genitalium is a sexually transmitted micro-organism which has the potential to cause clinical disease; in men more so than women. Although it was first identified in men with NGU in 1980 much remains unclear about the natural history of untreated infection. While there is clear association with NGU in men the clinical evidence that it causes epididymo-orchitis, proctitis,

reactive arthritis and facilitates HIV transmission in men is weak, although biological plausible. It is not known how long asymptomatic infection persists in untreated men, nor the risk of developing disease if left untreated. Although there is evidence of sexual transmission from male to female, it is unclear how often this occurs and of the risk of developing reproductive tract disease.

With the advent of commercially available tests in some countries but not the United States, *M. genitalium* diagnosis is now possible in some settings. However, the cost effectiveness of screening and diagnostic testing using *M. genitalium* NAAT testing has not been evaluated in randomised trials. Undertaking and interpreting such clinical studies will be complex as macrolide antimicrobial resistance is now common in many countries most likely due to the widespread use of azithromycin 1 g to treat STIs and flouroquinolone resistance is beginning to emerge.[1-4] This emphasises the importance of adopting the principles of good antimicrobial stewardship, including the use of accurate diagnostics (https://www.nice.org.uk/guidance/ng15/chapter/1-Recommendations#terms-used-in-this-guideline) and undertaking a test of cure, when considering how best to manage this infection in clinical practice.[2]

In this review article the evidence available on the epidemiology, clinical presentation and natural history in men is examined. The review article also examines the potential benefits of utilising *M. genitalium* NAAT testing in a diagnostic setting with and without antimicrobial resistance testing not only in managing the patient but its potential role in informing partner notification and treatment.

Epidemiology

There are two large population based survey studies of *M. genitalium* available that have provided us with unbiased information on the epidemiology of this emerging sexually transmitted pathogen in asymptomatic men.[5, 6] The first of these was based on Wave III of the National Longitudinal Study of Adolescent Health in the USA. Young adults between the ages of 18 and 27 years were enrolled

between 2001-2002. *M genitalium* prevalence in men was 1.1% and 0.8% in women, with an overall prevalence of 1.0%. In contrast the prevalences of chlamydial, gonococcal and trichomonal infections were 4.2%, 0.4% and 2.3% respectively. After adjustment for other risk factors *M. genitalium* infection was strongly associated with increasing numbers of sexual partners and black race. The second study was a probability sample survey in Britain: The National Survey of Sexual Attitudes and Lifestyles (NATSAL-3) conducted between 2010 and 2012 among sexually experienced men and women between the ages of 16 and 44. In this study, the prevalence of *M. genitalium* in men was 1.2% and in 1.3% in women. Risk factors for *M. genitalium* infection included black race, increased numbers of total and new sex partners, and unsafe sexual practices. A smaller population based survey of young men aged 21-24yrs from Aarhus County, in Denmark 1997-98 observed a similar prevalence of 1.1% and an association with increasing number of sexual partners.[7]

Among males the most common clinical manifestation of *M. genitalium* infection is NGU. It is currently unknown what proportion of men infected with *M. genitalium* develop NGU but is probably only a minority. If we assume a duration of infection of 1 year we can estimate using data from England in 2011 that approximately 6500 (5.2%) of 125,000 men *M. genitalium*-positive men developed NGU. [8-12] Totten and McGowin in this supplement review mechanisms of persistence and immune evasion by *M. genitalium* which enable it to establish chronic and persistent infection.[13] Women can resolve infection spontaneously and it is likely men can as well. The duration of infection in women varies from a few months to over a year however we do not know the duration of infection in men.[14-17]

The proportion of cases caused by *M. genitalium* varies geographically and by socio economic status. *Neisseria gonorrhoeae* is the most common cause of urethritis in most developing regions of the world.[18] *Chlamydia trachomatis* is the most common pathogen associated with NGU followed by *M. genitalium* and in the USA *Trichomonas vaginalis.*[19-21] *M. genitalium* can also cause infection in men with gonococcal urethritis though, *C. trachomatis* is more common.[18, 22] *M. genitalium* is

now recognized as the dominant organism associated with persistent NGU following treatment of NGU.[19]

Survey studies of men-who-have-sex-with-men (MSM) reveal higher rates of all STIs than observed in population based surveys. In a survey of MSM attending sauna's in Australia, Bradshaw et. al.[23] found the prevalence of *M. genitalium* to be 2.1% compared to prevalence rates of 8.1% for *C. trachomatis* and 4.8% for *N. gonorrhoeae*. Importantly, all organisms were significantly more common in the rectum than in either the urethra or the pharynx. These findings have been replicated in several other studies of different MSM populations.[24-26] Of interest, *C. trachomatis* and *M. genitalium* prevalence rates are lower among MSM with NGU than in heterosexual men with a higher proportion of NGU cases are idiopathic in MSM.[27,28] Soni et. al.[24] found that *M. genitalium* was more prevalent in men with HIV infection while the prevalence of *C. trachomatis* and *N. gonorrhoeae* was not influenced by HIV status. If supported this finding may provide clues to key differences in the host immune response to these organisms.

In summary, *M. genitalium* is one of the major causes of NGU worldwide but an uncommon sexually transmitted infection (STI) in the general population. Infection in men is usually asymptomatic and it is likely most men resolve infection without developing disease.

Immunopathogenesis: NGU and proctitis

M. genitalium is a slow growing micro-organism which can replicate both intracellularly and extracellularly and is able to establish chronic infections. [29] During chronic epithelial cell infection it produces pro-inflammatory cytokines which predominantly consist of potent chemotactic and/or activating factors for phagocytes.[30] This is discussed in more detail by Totten and McGowin in this supplement.[13]

Sexual transmission

Although it is now well established that *M. genitalium* is sexually transmitted it is not known how often this occurs per episode of unprotected sexual intercourse.[29] Estimates for chlamydial transmission from men to women per episode of vaginal coitus have been based on observational studies and range from 10% to 39.5% with the lower estimate based on a recent transmission dynamic mathematical model using the dyad study of Quinn et al.[31-33] Studies of sexual dyads suggest that transmission is probably lower than that for *C. trachomatis* which would be consistent with lower infectious load of *M. genitalium* compared to *C. trachomatis*.[33-35] It is likely that men with symptomatic NGU and presumably higher *M. genitalium* loads may be more infectious than men with asymptomatic infection. [34, 36-38] Studies of both *C. trachomatis* and *M. genitalium* in older men also provide additional insights into the relative transmission dynamics of these commonly associated STIs. Napierala et al.[39] tested for *M. genitalium* in 2,750 preserved specimens originally submitted to a reference laboratory for *C. trachomatis* testing from STI and community clinics including men ranging in age from adolescents to those greater than 60 years of age. As has been shown in numerous STI clinic based studies, the highest prevalence of *C. trachomatis* infection was in the <20 age group with a progressive prevalence decrease to very low levels among individuals greater than 40 years of age. In contrast the age group with the highest prevalence of *M. genitalium* was in the 20 to 30-year-old age group. Though *M. genitalium* prevalence rates decreased in the above 30 age groups the decline was not as steep as was observed for *C. trachomatis* and, strikingly, among men >40, *M. genitalium* was more common than *C. trachomatis*. These findings were corroborated by the NATSAL-3 population based survey.[5, 40] Taken together these observations suggest the hypothesis that the average duration of *M. genitalium* infection in men is longer than the average duration of *C. trachomatis* infection while the lower prevalence of *M. genitalium* infection in younger males compared to *C. trachomatis* provides

further support for the hypothesis that infectivity of *M. genitalium* is lower than that of *C. trachomatis*.

As carriage of *M. genitalium* in the oro-pharynx appears to be very uncommon, transmission through oral sex is likely to be rare.[41, 42] It is unknown whether risk of transmission differs between anal and vaginal intercourse.

***Mycoplasma genitalium* and NGU**

Given that *M. genitalium* was first identified in men with NGU and that it induces the release of pro-inflammatory cytokines it is not surprising that *M. genitalium* has been strongly and consistently associated with NGU.[29, 30] Taylor-Robinson and Jensen in 2011 reviewed all the published literature and observed that *M. genitalium* has been detected in 15 to 25% of men with symptomatic NGU, compared to about 5 to 10% of those without disease (OR 5.5 (95% CI:4.3-7.0))[29]. In several studies, the clinical characteristics of symptomatic NGU have not been shown to identify the pathogen specific aetiology. [20, 21, 43]

Incubation period of NGU

The recommended period for contact tracing in men presenting with NGU ranges from 4 weeks to 60 days from the onset of symptoms. [19, 44] For the European guideline this is based on the assumption that the incubation period for chlamydial NGU is 2-4 weeks. Although the incubation period for the development of *M. genitalium* NGU is unknown, it is likely that *M. genitalium's* slow replication rate compared to chlamydia would result in a more prolonged incubation period before NGU develops.[29] Thus, while, the limited evidence available suggests this could be up to 60 days, it may be potentially even longer.[30] Comparison of infectious disease epidemiology in men with chlamydia and *M. genitalium* in NGU studies may provide insights as to whether this is the case. However, there are a number of biases which make these data difficult to interpret including high

risk behaviour of controls and attendance as a result of being a contact of an STI.[9, 20] Nevertheless, in the case control study by Leung et al. men with *M. genitalium* NGU were no more likely to have had a new partner or more than one partner compared to controls whereas chlamydial NGU was associated with these behavioural risk factors.[9] Wetmore et al. observed that the mean duration of relationship for the most recent partner for men with NGU was longer for *M. genitalium*-positive men (mean – 75 days) than for chlamydia-positive men (mean - 16 days). [21] These data provide additional support for the hypothesis that the infectivity of *M. genitalium* is less than that of *C. trachomatis*.

Definition of NGU and initiating treatment

There are two working definitions of NGU used in clinical practice.[19, 44] While both include the presence of urethral discharge, dysuria and/or urethral irritation and the requirement for objective evidence of urethral inflammation, the European guideline uses $\geq$ 5 PMNLs /high power field (x1000) (PMNLs/hpf) on a stained urethral smear and the U.S. CDC guideline uses $\geq$ 2 PMNLs/hpf.[19, 44] Treatment using a lower cut-off may result in over treatment of many men with low grade urethritis (2-4 PMNLs/hpf) who do not have an infection (see below). In Europe it is recommended that symptomatic men with <5 PMNLs/hpf are reassured and asked to return for an early morning smear if their symptoms do not settle and their NAAT tests for *C. trachomatis* and *N. gonorrhoeae* are negative.[19] This is because some men with low grade urethritis will have been misclassified because of the inaccuracy of the urethral smear .[8] There is currently no evidence of significant morbidity in symptomatic chlamydia and gonorrhoea NAAT-negative men with <5 PMNLs/hpf on a urethral smear who are reassured and do not receive anti-microbial therapy. Many of these men get better without treatment. [19]

While reducing the PMNL count cut-off will increase the number of men identified and treated for presumptive chlamydia or *M. genitalium* infection it will also disproportionately increase the number of men (and their partner(s)) without a sexually transmitted infection, diagnosed and treated for NGU. Figure 1 is a theoretical representation of the distribution of urinary leucocytes (ULs) of high risk men infected with *M. genitalium.* This representation is based on the findings of Wiggins et al who investigated the UL distribution in 87 high risk men presenting to a GUM department.[45] These men were tested for *C. trachomatis*, *N. gonorrhoeae* and urethritis but not M. *genitalium.* A previous study in the same population had demonstrated that *M. genitalium* prevalence was about half that of *C. trachomatis* and the observations of Moi et al indicate that the inflammatory response is less marked.[9, 46] As the UL count and the PMNLs/hpf are correlated, changes in the UL count can be used to explore how changes in the urethral smear cut-off will effect detection of *C. trachomatis*, *N. gonorrhoeae* and *M. genitalium.* [45,46 When the UL threshold (see figure, threshold A), which approximated the urethral smear cut-off 5pmns/hpf in the study is lowered (see figure - threshold B) more high risk men in the population tested for urethritis with *M. genitalium, C. trachomatis* and *N. gonorrhoeae* will be identified. However, the specificity of urethritis for detecting men with these infections will also decrease and, as the cell count threshold is reduced, disproportionately more high risk men (and their partners) with no infection compared to those with an infection will require treatment as a result of being diagnosed with NGU. This would also be expected to be the case with a urethral smear. [45-47] While other infections such as *Ureaplasma urealyticum* or *Trichomonas vaginalis* (in populations where this micro-organism is prevalent) can account for some cases, the specific aetiology in men not infected with STI pathogens is unclear.[19] This concept is also consistent with the observations that idiopathic NGU has a lower mean leucocyte count compared to men in whom an infection is detected.[20, 21, 43]

In summary, reducing the PMNL count cut-off from $\geq$ 5 to $\geq$ 2 to for diagnosing NGU will increase the number of men identified and treated for presumptive chlamydia or *M. genitalium* infection but

will also disproportionately increase the number of men (and their partner(s)) without a sexually transmitted infection, diagnosed and treated for NGU.

NAAT testing for M. genitalium in men with symptoms of NGU

Currently, NAAT testing is not available in many centres but anticipated over the next few years. The European NGU guideline advises that *M. genitalium* NAAT testing, preferably with macrolide resistance testing in men with NGU is likely to be cost effective, as this would enable the implementation of more effective treatment strategies. It is also likely that testing symptomatic men, who do not meet the PMNL NGU diagnosis criteria, for STI pathogens including *M. genitalium* and withholding treatment pending the results would reduce unnecessary antimicrobial therapy. Whether or not testing STI pathogen-NAAT negative, in this group of men, would reduce re-attendance for an early morning smear and/or the persistence of symptoms, as currently recommended in Europe, remains to be demonstrated. (see Table)

Retesting men if M. genitalium NAAT-positive

The European guideline recommends that all persons testing *M. genitalium* NAAT-positive should be retested at the earliest 3 weeks after commencement of therapy due to the high prevalence of macrolide resistance either present pre-treatment or developing during treatment with azithromycin.[2] Many patients enter a stage of few or no symptoms after treatment, but with persistent carriage and subsequent risk for spread of resistance in the community.[2]

Antimicrobial therapy for acute NGU

The European 2016 NGU treatment guideline recommends that azithromycin 1g not be used as first line therapy, due to the accumulating evidence that this regimen promotes macrolide antimicrobial resistance in *M. genitalium* and is only 87% effective in eradicating macrolide sensitive infection.[1,

4, 19] This is contrary to the 2015 CDC STD Treatment Guidelines and United Kingdom 2015 NGU treatment guidelines which recommend azithromycin 1 g for NGU.[44, 48] These differences in treatment approach reflects how rapidly the evidence base concerning treatment of *M. genitalium* is changing. Given the new evidence and the imperative of good antimicrobial stewardship the continued recommendation of azithromycin 1g as first line treatment for NGU in the USA and the UK should be reviewed. [44, 48, 49] There is some evidence that in macrolide sensitive infection azithromycin 500mgs followed by 250mgs for 4 days may be more effective and less likely to promote macrolide antimicrobial resistance, particularly if prescribed after a 7 day course of doxycycline. [19, 50-52] However a recent retrospective study from Australia suggests that the extended azithromycin regimen may not be more effective than 1g and also may be associated with promotion of macrolide antimicrobial resistance.[4, 53] It is unclear why the observations differ and may reflect differences in the populations studied with the latter including high risk men who have sex with men in whom three quarters of pre-treatment *M. genitalium* strains are macrolide resistant.[53]

The European guideline recommends doxycycline 100mgs bid for 7 days as first line therapy for NGU.[19] It is effective against chlamydia and, although it has markedly reduced efficacy against *M. genitalium* in treatment of wild-type infection compared to azithromycin 1g, it does not appear to promote tetracycline resistance. It also has the potential benefit of reducing bacterial load which would theoretically reduce the risk of selection for both macrolide and quinolone resistance as a result of heterotypic resistance if these antimicrobials are subsequently prescribed in men who fail therapy.[54, 55] This is supported by the observational data from Anagrius et al. and Gesink et al. in which no macrolide antimicrobial resistance developed with the extended azithromycin after pre-treatment with doxycycline.[50, 52] Doxycycline efficacy also would not be affected by the presence of macrolide resistance, thus some macrolide resistant infections will also be eradicated.

In summary, the recommendation of Azithromycin 1 g as first line treatment for NGU by the USA and the UK should be reviewed. Given the recent conflicting evidence on the efficacy of the extended 5

day regimen as first line therapy, it may be that Doxycycline 100mgs bd for 7 days is the most logical choice for use as first line therapy.

New investigational antimicrobials and combination therapy

Increasing rates of *M. genitalium* treatment failure due to antimicrobial resistance have resulted in an urgent need for new therapies which Bradshaw et al discuss in detail elsewhere in this supplement.[4]

Management of persistent or recurrent NGU following initial treatment

In 15-25% of men, persistent or recurrent symptoms can occur. While *M. genitalium* is an important cause, other aetiologies such as *Trichomonas vaginalis* need to be considered. The management of persistent or recurrent NGU can be challenging particularly in the absence of diagnostic testing for *M. genitalium*.[19] In men initially treated with doxycycline, the extended 5 day azithromycin regimen is recommended by the European Guidelines. [19] The 2015 CDC STD Treatment guidelines recommend azithromycin 1g if the patient was initially treated with doxycycline which given the recent change in the evidence base should be reviewed.[44, 49] If azithromycin had been used as first line therapy, then moxifloxacin 400mgs daily for 7-14 days is recommended [19, 44] although quinolone antimicrobial resistance is also beginning to emerge.[2, 4] A possible alternative approach in treatment failures initially treated with azithromycin, although not recommended in either the European or CDC Treatment Guidelines is the use of doxycycline as second line therapy. Doxycycline is 30-40% effective in eradicating *M. genitalium* irrespective of whether or not it is macrolide and/or quinolone resistant.[2, 4]Moreover, doxycycline is significantly cheaper than moxifloxacin and may be safer.

In Europe the concurrent administration of metronidazole is recommended in all men with NGU who fail 1st line therapy, whereas in the United States this is only recommended in men who have sex with women where *Trichomonas vagi*nalis is prevalent.[19, 44]

In summary, the management of persistent and recurrent NGU is challenging in the absence of *M. genitalium* NAAT and antimicrobial resistance testing.

Partner notification and management

Men with NGU.

The primary aims of partner notification and treatment are to prevent re-infection of the index male, prevent complications of the infection in the partner(s) and reduce onward transmission. All current partner(s) should be tested and treated with the same treatment as the index patient and advised not to be sexually active until all have completed treatment and symptoms have resolved.[2, 19] This should be undertaken sensitively considering socio-cultural issues and avoiding stigma.[19] This is a complex issue given the limited availability of *M. genitalium* NAATs, the poor efficacy of current first-line treatment regimens, the prevalence of *M. genitalium* macrolide resistance globally, and the observation that not all sexual partners are infected. The issue is even more complicated for other non-current partners in the three months prior to the index male's diagnosis. Table 1 details the advantages of *M. genitalium* NAAT testing with or without antimicrobial resistance (AMR) testing in managing partners of men presenting with symptoms of NGU. In the United States there is no diagnostic test for *M. genitalium* that is cleared by the FDA for commercial use.

In summary, current sexual partners should be tested and treated with the same treatment as the index patient.

Persistent and recurrent NGU

It is currently recommended that all recent sexual partner(s) (see above) should be tested for chlamydia and gonorrhoea using a NAAT and offered treatment.[19, 44] In men with persistent NGU,

in whom *M. genitalium* is common, in the absence of specific *M. genitalium* diagnostic testing it is unclear whether the partner should be retreated. It is likely that re-treatment of the sexual partner with the same antimicrobial therapy effective in the index case will be beneficial if persistent/recurrent NGU in the index case resolves following extended therapy, but subsequently recurs following sexual intercourse.[19]

Other clinical syndromes potentially associated with *M. genitalium*

Proctitis

Proctitis is characterized clinically as rectal pain and/or rectal discharge. There is one large study that demonstrates the association of *M. genitalium* with proctitis. Among 154 Australian MSM with proctitis Bissessor et al [56] reported a *M. genitalium* prevalence of 12%, *N. gonorrhoeae* – 25%, chlamydia– 19% and herpes simplex virus – 18%. *M. genitalium* was the only bacterial infection significantly associated with HIV infection in this study. Soni et al made the same observation in a survey of asymptomatic rectal carriage of STI pathogens. [24] Bissessor et al [56] also found that the rectal *M. genitalium* bacterial load was significantly higher in men with proctitis compared to asymptomatic men. This finding parallels the results of quantitative studies of *M. genitalium* in urethral infections, however treatment outcomes were not evaluated. There are no specific studies that have evaluated treatment effectiveness for *M. genitalium* proctitis.

Prostatitis

There is some data on the association of *M. genitalium* and prostatitis. Krieger et al. [557] reported that biopsies from 4% of 135 men with chronic prostatitis were positive by PCR for *M. genitalium.* Mo et al [58] recently described evaluation of 235 Chinese men with prostatitis and 152 asymptomatic STI clinic controls who underwent the same specimen collection procedures including

prostate massage. Using a quantitative *M. genitalium* PCR assay 10% of men with clinical prostatitis had evidence of *M. genitalium* infection of the prostate based on detection of the organism only in expressed prostatic secretions and/or the post prostatic massage urine specimen or 4 fold higher *M. genitalium* DNA concentrations in these specimens relative to concentrations in first or mid-stream urine specimens. Only 3% of controls had evidence of *M. genitalium* in the prostate (P = 0.005). These data suggest that *M genitalium* can be a cause of prostatitis in a small proportion of cases but this requires confirmation.

Epididymitis

Given the parallels between clinical syndromes caused by *C. trachomatis* and *M. genitalium* it would be expected that *M. genitalium* may result in epididymitis would result from infection. Hamasuna [59] described a patient with classic epididymitis from whom *M. genitalium* was the only known pathogen identified. There was no clinical response to minocycline and cephalosporin antibiotics but improvement was noted following the administration of levofloxacin. Ito et al [60] recently reported on 56 cases of epididymitis in men less than 40 years old. *C. trachomatis* was associated with 50% of the cases while *M. genitalium* was present in 8%. Although there is limited data, *M. genitalium* may cause epididymitis though less commonly than *C. trachomatis.*

Syndromes possibly associated with M. genitalium

Given the association of *C. trachomatis* with post infectious arthritis, there is a possibility that *M. genitalium* would be associated with this or other syndromes involving joint inflammation. [61, 62] Although Horner *et al* had reported that *M. genitalium* is associated with balano-posthitis such an association was not observed in the recent study by Ito *et al.*[43, 63]

HIV transmission

M. genitalium infection is associated with HIV acquisition in women [64] which may be due to its ability to induce a pro-inflammatory response. Genital tract infections can cause an inflammatory discharge which has been associated with increased HIV shedding.[65] Whether *M. genitalium* infected men practising unprotected anal intercourse may be more likely to be at an increased risk of HIV acquisition and, if HIV infected, more likely to transmit HIV during unprotected anal and insertive oral intercourse is as yet unknown. The inflammatory response associated with *M. genitalium* infection in men is less marked than that observed with chlamydia and gonorrhoea and one small study of men with NGNCU (*M. genitalium* was not tested for) did not demonstrate an increase in HIV load in the semen compared to controls. [66]

Screening for *M. genitalium* in men

In the absence of randomised controlled trials demonstrating cost effectiveness, screening asymptomatic men cannot be recommended.

Conclusion

M. genitalium is one of the major causes of NGU worldwide but an uncommon sexually transmitted infection in the general population. Effective treatment is complicated as macrolide antimicrobial resistance is now common in many countries, conceivably as a result of widespread use of azithromycin 1g to treat STIs, and the limited availability of diagnostic tests for *M. genitalium*. Improved outcomes in men with NGU and better antimicrobial stewardship are likely to arise from introduction of diagnostic *M. genitalium* NAAT testing including antimicrobial resistance testing in men with symptoms of NGU as well as in their current sexual partner(s). The cost effectiveness of these approaches need further evaluation.
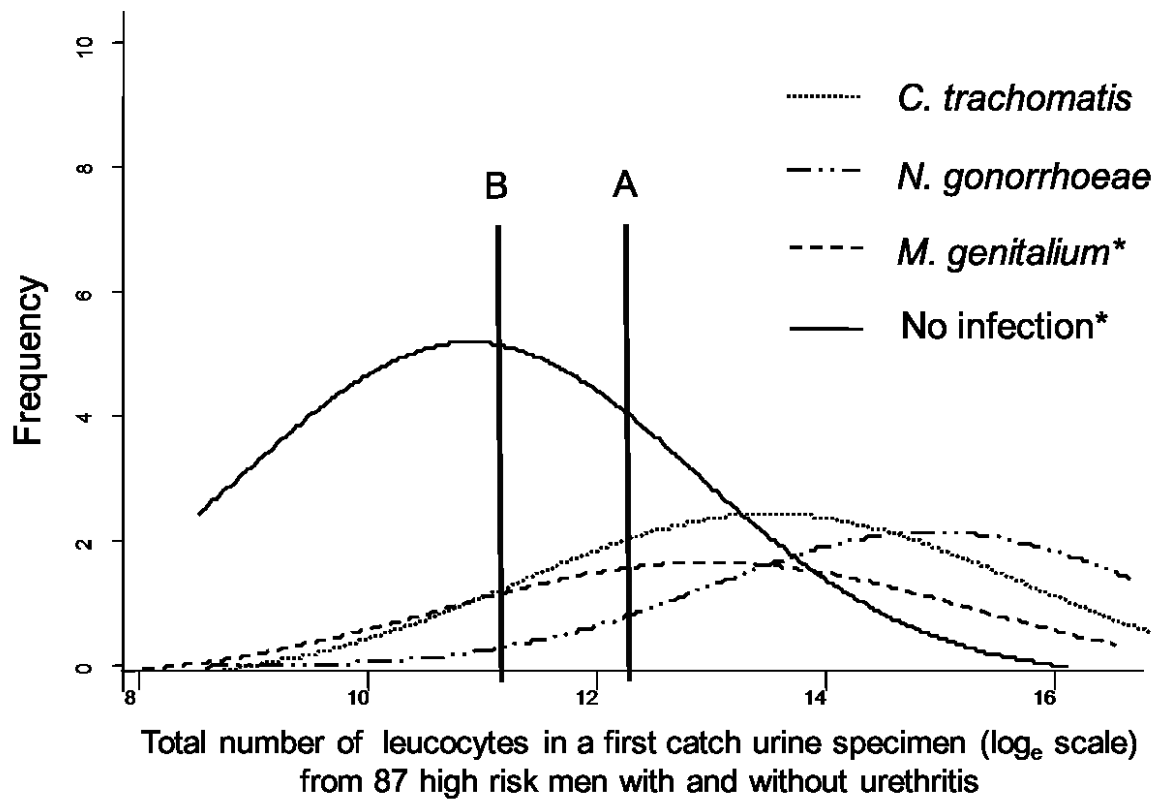
Figure 1 Hypothetical frequency distribution of urinary leucocyte counts for *M. genitalium** and no infection* in high risk men presenting to a department of GUM who were tested for *C. trachomatis* and *N. gonorrhoeae*. Line A correlates with the urethral smear cut-off of 5 PMNLs /hpf for NGU and line B demonstrates the effect on sexually transmitted infection detection if the cut-off is decreased. Adapted from Wiggins et al.[45]

		No *M. genitalium* NAAT testing following European guidelines	No *M. genitalium* NAAT testing following CDC guidelines	*M. genitalium* NAAT testing plus knowledge of local AMR[1] prevalence	*M. genitalium* NAAT testing plus macrolide AMR testing and knowledge of local quinolone AMR prevalence	*M. genitalium* NAAT testing plus macrolide and quinolone AMR testing
Symptoms of NGU	**Management**	NAAT test for CT[2] and NG[3] and confirm patient has NGU based on $\geq$ 5 PMNLs/hpf	NAAT test for CT and NG and confirm patient has NGU based on $\geq$ 2 PMNLs/hpf	Confirm man has NGU on microscopy[4]	Confirm man has NGU on microscopy[4]	Confirm man has NGU on microscopy[4]
	Advantages / disadvantages	Unable to reassure if low grade urethritis <5 PMNLs/hpf[5]	More CT infected men are treated but disproportionately greater increase in treatment of men with no infection (Figure 1)	Able to reassure if low grade urethritis <5 PMNLs/hpf[6]	Able to reassure if low grade urethritis <5 PMNLs/hpf[6]	Able to reassure if low grade urethritis <5 PMNLs/hpf[6]
Confirmed NGU	**Management**	Doxycycline 100mgs bd 7 days	Azithromycin 1 g or Doxycycline 100mgs bd 7 days	Doxycycline 100mgs bd 7 days (European guideline)	Doxycycline 100mgs bd 7 days (European guideline)	Doxycycline 100mgs bd 7 days (European guideline)
	Advantages / disadvantages	Does not reduce antimicrobial therapeutic options if treatment is not effective	Azithromycin 1 g associated with development of macrolide AMR in *M. genitalium*	Does not reduce antimicrobial therapeutic options if treatment is not effective	Does not reduce antimicrobial therapeutic options if treatment is not effective	Does not reduce antimicrobial therapeutic options if treatment is not effective
Contacts of NGU	**Management**	NAAT test for CT and NG then Doxycycline 100mgs bd 7 days	Azithromycin 1 g or Doxycycline 100mgs bd 7	Doxycycline 100mgs bd 7 days and test for *M. genitalium*[4]	Doxycycline 100mgs bd 7 days and test for *M. genitalium*[4]	Doxycycline 100mgs bd 7 days and test for *M. genitalium*[4]

		days				
	Advantages / disadvantages	Does not reduce antimicrobial therapeutic options if treatment is not effective	Azithromycin 1 g associated with development of macrolide AMR in *M. genitalium*	Does not reduce antimicrobial therapeutic options if treatment is not effective	Does not reduce antimicrobial therapeutic options if treatment is not effective	Does not reduce antimicrobial therapeutic options if treatment is not effective
Persistent/ recurrent NGU	**Management**	Azithromycin 5 day regimen[7] plus metronidazole 400mgs bd 5 days	Moxifloxacin 400mgs of 7 days if treated with azithromycin 1 g initially; Azithromycin 1 g if initial treatment doxycycline 100mgs bd 7 days. Plus metronodazole/ Tinidazole 2g if partner(s) female and *T. vaginalis* prevalent	Azithromycin 5 day regimen[7] if *M. genitalium* negative. If *M. genitalium* positive choice of azithromycin or moxifloxacin to be guided by local prevalence of macrolide and quinolone AMR. Plus metronidazole[8]	Azithromycin 5 day regimen[7] if *M. genitalium* negative. If *M. genitalium* positive choice of azithromycin or moxifloxacin to be guided by macrolide AMR result and knowledge of local prevalence of quinolone AMR. Plus metronidazole[8]	Azithromycin 5 day regimen[7] if *M. genitalium* negative. If *M. genitalium* positive, choice of azithromycin or moxifloxacin to be guided by macrolide and quinolone AMR result. Plus metronidazole[8]
	Advantages / disadvantages	Likely to be effective unless macrolide resistant *M. genitalium* aetiology of NGU	Moxifloxacin effective against macrolide AMR *M. genitalium*. Azithromycin 1 g associated with development of macrolide AMR in *M. genitalium*	Improved cure rates following second line therapy	Improved cure rates following second line therapy	Improved cure rates following second line therapy
M.	**Management**	Test of cure: Not possible	Test of cure: Not possible	Test of cure $\geq$ 3 weeks after start	Test of cure $\geq$ 3 weeks after	Test of cure $\geq$ 3 weeks after start of

				of treatment	start of treatment	treatment
genitalium detected	**Advantages / disadvantages**	Risk of spread of resistant strains which have developed following treatment	Risk of spread of resistant strains which have developed following treatment	Prevents spread of resistant strains which have developed following treatment but are asymptomatic	Prevents spread of resistant strains which have developed following treatment but are asymptomatic	Prevents spread of resistant strains which have developed following treatment but are asymptomatic
Contacts of persistent/ recurrent NGU	**Management**	No further treatment	No further treatment	Treatment guided by NAAT results of tests prior to epidemiological treatment	Treatment guided by NAAT results of tests prior to epidemiological treatment	Treatment guided by NAAT results of tests prior to epidemiological treatment
	Advantages / disadvantages	At risk of re-infection if *M. genitalium* aetiology of NGU	At risk of re-infection if *M. genitalium* aetiology of NGU	Reduced risk of re-infection and inappropriate additional antimicrobial therapy	Reduced risk of re-infection and inappropriate additional antimicrobial therapy	Reduced risk of re-infection and inappropriate additional antimicrobial therapy
Antimicrobial stewardship		not good	poor	good	very good	very good

[1]Antimicrobial resistance; [2] *Chlamydia trachomatis*; [3] *Neisseria gonorrhoeae*; [4] Assumes NAAT testing for Chlamydia, gonorrhoea which would also include trichomonas depending on local population prevalence; [5] Men are invited back for an early morning smear after holding their urine over night if symptoms do not settle and CT and NG NAAT-negative; [6] Reassurance in these cases would be based on negative NAAT-tests for *M. genitalium*, CT, NG +/- trichomonas; [7]Azithromycin 500mgs stat then 250mgs for 4 days; [8] If trichomonas NAAT-positive. Metronidazole 400mgs bid 5 days currently recommended for treatment of possible bacterial vaginosis associated bacteria in European guideline[8] but benefit is unclear.

Table 1 Exploring potential benefits associated with *M. genitalium* NAAT testing with or without antimicrobial resistance (AMR) testing in men presenting with symptoms of NGU compared to current standards of care.

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