British Association for Sexual Health and HIV national guideline for the management of infection with *Mycoplasma genitalium* (2018)

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Introduction

This is the first British Association of Sexual Health and HIV (BASHH) guideline for the diagnosis and management of *Mycoplasma genitalium* in people aged 16 years and older. The guideline is primarily aimed at level 3 sexually transmitted infection (STI) management services within the UK, although it could also serve as a reference guide for STI services at other levels.

Whilst the guideline sets out recommendations for best practice according to current evidence, it is acknowledged that not all clinics will have access to *M. genitalium* testing at the time of guideline publication. The objective of this guideline is therefore also to assist clinics and laboratories in making the case for funding towards *M. genitalium* testing by underlining the importance of testing in relevant populations.

Editorial Independence

This guideline was commissioned and edited by the Clinical Effectiveness Group (CEG) of BASHH, which also provided funding for a literature search. No other or external funding was obtained.

Conflict of Interest

All authors have signed BASHH CEG Conflict of Interest forms declaring no conflict of interest at the time of writing.

Rigour of development

This guideline was produced according to specifications made in the CEG's document '2015 Framework for guideline development and assessment' accessible at http://www.bashh.org/documents/2015%20GUIDELINES%20FRAMEWORK.pdf

Search strategy

The writing group determined PICO (Patient, Intervention, Comparison, Outcome) questions which formed the basis for the literature search. The questions are listed in Appendix 1.

A search was conducted using Medline, Embase, the Cochrane library and NHS Evidence. The search heading was kept broad ("genitalium") to include all the guideline questions. Only publications in the English language were considered. Age, country and study design limits were included in the PICO criteria, except that studies from Japan were considered for questions 8, 9 and 10 because it was felt that evidence in these studies, particularly with respect to resistance and treatment issues, would contribute significantly to and inform the guideline (see Appendix 1). 'Grey literature' included conference abstracts from IUSTI, BASHH, BHIVA, ICAAC, ASHM, ECCMID in the last three years. The

writing group used a modified GRADE system for assessing evidence and formulating recommendations.

Equality impact assessment

An assessment of the guideline recommendations was made according to the principles of the NICE equality policy (Appendix 2).

Stakeholder involvement, piloting and feedback

The draft guideline recommendations were presented at the joint British HIV Association and BASHH annual conference 2018. The draft guideline was appraised by the CEG using the AGREE instrument, posted on the BASHH website for a consultation period of 2 months, and piloted in a sample of clinics. In response to the consultation, suitable amendments were made to the guideline and the final draft was submitted to the CEG. The patient information leaflet (PIL) was reviewed by the CEG, BASHH patient and public panel, and also piloted in a sample of clinics and comments were reviewed and incorporated where appropriate.

The writing group consisted of genitourinary medicine physicians with experience in managing *Mycoplasma genitalium* (SS, MR, NPS, PH), a consultant microbiologist (HF), a pharmacist (NN), a sexual health advisor (AP) and two patient representatives (DB, CP).

The guideline will be updated every five years according to the BASHH CEG guideline framework. This interval could be shorter should new data arise which could significantly impact recommendations.

Patient and Public Involvement

Two patient representatives attended a writing group meeting, contributed to the design and written content of the PIL and commented on the draft guidelines. The guideline was also reviewed by the BASHH Patient and Public Panel.

Summary of Recommendations

Section	Recommendation	Grading
4.1	Test for *M. genitalium* infection in all males with non-gonococcal urethritis	1B
4.1	Test for *M. genitalium* infection in all individuals with signs and symptoms suggestive of pelvic inflammatory disease	1B
4.2	Test current sexual partners of persons infected with *M. genitalium*	1D
5.2	First void urine is the specimen of choice in males	1C
5.2	Vaginal swabs (clinician- or self-taken) are the specimen of choice in females	1C
5.2	All *M. genitalium* positive specimens should be tested for macrolide resistance mediating mutations	1B
6.2	Treatment regimens for uncomplicated infection: Doxycycline 100mg two times daily for 7 days followed by azithromycin 1g orally as a single dose then 500mg orally once daily for 2 days Moxifloxacin 400mg orally once daily for 10 days	 1D 1B
6.3	Treatment regimens for complicated infection: Moxifloxacin 400mg orally once daily for 14 days	 1D
6.5	Alternative treatment regimens: Doxycycline 100 mg two times daily for 7 days followed by pristinamycin 1g orally four times daily for 10 days Pristinamycin 1g orally four times daily for 10 days Doxycycline 100mg orally twice daily for 14 days Minocycline 100mg orally twice daily for 14 days	 2C 2C 2C 2D
6.11	All patients should attend for a test-of-cure five weeks (and no sooner than three weeks) after the start of treatment to ensure microbiological cure	1D

1. Microbiology

Mycoplasma genitalium was first isolated in 1981, having been cultured from urethral specimens of two men presenting with non-gonococcal urethritis (NGU).[1] *M. genitalium* belongs to the Mollicutes class,[2] and with a genome of only 580 kilobases in size, is the smallest known self-replicating bacterium. It lacks a cell wall, and hence is not visible by Gram stain. The organism is fastidious and typically requires weeks or months to culture.

M. genitalium has been detected from genito-urinary, rectal and respiratory tract specimens, but carriage in the throat seems to be rare.[3] Although it was initially thought that disease appeared to be limited to the genito-urinary tract, there is some evidence it could potentially cause proctitis.[3-5] The specialised tip-like structure of *M. genitalium* enables it to adhere to and invade epithelial cells.[3] The organism is able to evade the adaptive immune system possibly through both its ability to establish intra-cellular infection and by antigenic and phase variation of its surface-exposed proteins, and infection may persist for months or years.[3,6,7] Although the diseases associated with *M. genitalium* infection are thought largely to be as a result of the host immune response rather than organism-specific features, it has been demonstrated in human fallopian tube organ culture that infection can be directly toxic to cells resulting in cilial damage.[4,7,8]

2. Epidemiology

2.1 Prevalence in general population and risk factors for infection

Prevalence estimates for *M. genitalium* infection in men and women in the general population range from 1-2%, being slightly higher in women.[9-11] Similar to *C. trachomatis*, risk factors for *M. genitalium* infection include younger age, non-white ethnicity, smoking, and increasing number of sexual partners.[9-11] However, the prevalence of *M. genitalium* infection appears to peak later than that for *C. trachomatis*, particularly in men, and to remain higher in older age groups.[11-13] Amongst STI clinic attendees, prevalence ranges are higher, from 4-38%.[14-16]

2.2 Sexual transmission

In addition to the sexual behavioural risk factors above, sexual transmission is supported by the observation that sexual partners of individuals diagnosed with *M. genitalium* are more likely to be infected than controls.[17-19] Molecular epidemiological studies also support a sexual transmission model: in DNA-typing studies, sexual partners who were concurrently infected with *M. genitalium* frequently carry genetically identical strains.[20-22]

Transmission is primarily by genital-genital contact, but *M. genitalium* has also been detected in the ano-rectal compartment [5,23] and transmission by penile-anal contact has been established.[24] As carriage in the oro-pharynx is uncommon, the relative contribution of oral sex is likely to be very small.[25-27] The risk of transmission per coital act has yet to be determined but is likely to be less than that for chlamydia.[27]

2.3 Co-infection with other STIs

M. genitalium is associated with the detection of other bacterial STIs, *C. trachomatis* being the most frequently isolated co-organism.[28-31] An association between *M. genitalium* and HIV transmission and acquisition is biologically plausible and supported by some studies in sub-Saharan Africa.[32-34]

2.4 Clinical associations

2.4.1 Non-gonococcal urethritis

M. genitalium infection is unequivocally and strongly associated with NGU. Typically, the prevalence of *M. genitalium* in men with NGU is 10-20% and in male patients with non-chlamydial non-gonococcal urethritis (NCNGU) is 10-35%,[3] as compared to 1-2% in the general population.[11,35] In one meta-analysis of 19 observational studies examining *M. genitalium* infection with molecular techniques, 436/2069 patients with NGU (21.1%) were positive for *M. genitalium* versus 121/1810 controls (6.7%), yielding a pooled odds ratio of 3.8 [95% CI 3.0-4.9].[13] Further systematic reviews

have demonstrated a similar association, and demonstrated a yet stronger strength of association with NCNGU.[3] *M. genitalium* is also associated with persistent and recurrent urethritis, where up to 40% of patients may have *M. genitalium* detected.[36] A recent meta-analysis demonstrated an odds ratio of 26 for *M. genitalium* detection in men with persistent urethritis.[37]

2.4.2 *M. genitalium* in the female reproductive tract

Several studies support an association of *M. genitalium* infection in cisgender women with post coital bleeding and cervicitis, endometritis and pelvic inflammatory disease (PID).[11,18,38-41]

A recent meta-analysis has demonstrated significant associations between *M. genitalium* and cervicitis (pooled OR 1.66) and PID (pooled OR 2.14), in addition to pre-term birth and spontaneous abortion (pooled ORs 1.89 and 1.82 respectively).[42] *M. genitalium* is linked aetiologically to PID and accounts for 10-13% of cases of PID.[43,44] It has been shown to ascend from the lower to upper female genital tract,[3] has been detected frequently from endometrial biopsies in women with PID[45] and can cause epithelial cilial damage in human fallopian tube culture. However an association with tubal factor infertility has not yet been demonstrated and conducting studies to determine this will be difficult.[3,8,46]

2.4.3 Asymptomatic infection

The evidence suggests that the majority of people infected with *M. genitalium* in the genital tract do not develop disease.[27,47,48] Current treatments are imperfect and associated with development of antimicrobial resistance.[49,50] There is no evidence that screening asymptomatic individuals will be of benefit, and indeed is likely to do harm at a population level.[51]

Current asymptomatic partners (including non-regular partners where there is likely to be further sexual contact and risk of reinfection) of individuals with disease caused by *M. genitalium* infection should be tested and/or offered epidemiological treatment (using the same antimicrobial regimen as used in the index patient). This is to reduce the risk of re-infection in the index case.

3. Clinical Features

3.1 Signs and symptoms in males:[3]

None – the majority are asymptomatic[27]

Urethral discharge

Dysuria

Penile irritation

Urethral discomfort

Urethritis (acute, persistent, recurrent)

Balanoposthitis (in one study)[52]

3.2 Complications in males:

Sexually acquired reactive arthritis

Epididymitis

The clinical presentation of *M. genitalium* urethritis is similar to other causes and thus clinical features of acute symptomatic NGU cannot be used to determine the infective aetiology.[17,27,53-56] Although the proportion of infected men that develop symptoms is unknown this is likely to be <10%.[27]

Urethral discharge may be present spontaneously or on expression, and urethritis is confirmed by demonstrating five or more polymorphonuclear leucocytes (PMNLs) per high power (x1000) microscopic field (averaged over five fields with the greatest concentration of PMNLs) on a smear obtained from the anterior urethra.[57]

It is possible that sexually acquired reactive arthritis may occur as a result of *M. genitalium* infection.[3,27,58] An association with epididymitis is possible, but current data are lacking to support an association with prostatitis.[3] *M. genitalium* has been demonstrated at high prevalence in rectal samples from men who have sex with men (MSM) (particularly HIV-positive MSM), and one study suggesting a potential association showed that men with symptoms of proctitis had higher bacterial load of *M. genitalium* than those without rectal symptoms.[5,23] This warrants further investigation with larger studies.

3.3 Signs and symptoms in females

None – the majority are asymptomatic[18,40]

Dysuria

Post-coital bleeding

Painful inter-menstrual bleeding

Cervicitis

Lower abdominal pain (see Complications: PID)

3.4 Complications in females

Pelvic inflammatory disease

Tubal factor infertility (uncertain association)

Sexually acquired reactive arthritis

Pre-term delivery

Individuals with cervicitis due to *M. genitalium* frequently have no symptoms at all. If present, symptoms are nonspecific, with the most common symptom being post-coital bleeding.[59] Although the proportion of infected women that develop symptoms is unknown this is likely to be <5%.[47,48]

Examination is frequently normal, but on speculum examination the presence of mucopurulent cervical discharge, cervical friability and elevated numbers of PMNLs on cervical sample Gram staining are suggestive of infection.[18,38,40,60]

Clinical signs and symptoms of *M. genitalium*-associated PID are similar to, and indistinguishable from, PID due to *C. trachomatis.*

4. Recommendations for testing

4.1 Based on symptoms

- We recommend testing for *M. genitalium* infection in people with non-gonococcal urethritis (1B)
- We recommend testing for *M. genitalium* infection in people with signs and symptoms suggestive of pelvic inflammatory disease (1B)
- Consider testing for *M. genitalium* infection in people with signs or symptoms of muco-purulent cervicitis, particularly post-coital bleeding (2B)
- Consider testing for *M. genitalium* infection in people with epididymitis (2D)
- Consider testing for *M. genitalium* infection in people with sexually-acquired proctitis (2D)

4.2 Based on risk factors

- We recommend testing current sexual partners of persons infected with *M. genitalium* (1D)

There are currently insufficient data to recommend routine screening for *M. genitalium* infection in asymptomatic individuals. Asymptomatic individuals with confirmed chlamydia and/or gonorrhoea infection should not be routinely tested for *M. genitalium*.

Whilst the recommendation to test all men with NGU is clear, it is acknowledged that, at the time of writing, access to *M. genitalium* testing is limited and sending all specimens to Public Health England Reference laboratory for *M. genitalium* detection and/or determination of resistance status may not be cost viable. Given that some men clear *M. genitalium* with doxycycline treatment alone (for NGU), an alternative strategy would be to test men who remain symptomatic following doxycycline and use AMR-guided therapy to treat any positives. However this is not preferable because it would result in a longer patient journey and may miss infection in some individuals who become asymptomatic but who have not cleared infection.

5. Diagnosis

M. genitalium has fastidious nutritional requirements and is extremely slow growing therefore culture is not appropriate for diagnosis. Nucleic acid amplification tests (NAATs) that detect *M. genitalium* specific DNA or RNA in clinical specimens are the only useful diagnostic method. Several CE marked commercial tests are available, although none are currently FDA approved. Careful consideration of assay performance based on published data is essential, as the different NAATs are likely to have varying performance and lack extensive validation.[61] Local validation is required before the implementation of any test.

It is recommended that all *M. genitalium* positive specimens should be tested for macrolide resistance mediating mutations. Recently, commercial assays detecting macrolide resistance have become available. In the absence of local resistance testing, the Public Health England (PHE) Reference laboratory offers a molecular macrolide and fluoroquinolone susceptibility genotyping assay for specimens positive for *M. genitalium*. Currently there are no commercial assays available in the UK which detect mutations associated with fluoroquinolone resistance although these are likely to be available in the near future.

5.1 Specimen collection

The published data for the optimal specimen type is generally from small studies using a variety of different NAATs with different sensitivities, and which lack thorough validation; therefore the recommendations are based mainly on a practical approach to specimen collection.

5.1.1 Men

First void urine (FVU) is the most sensitive specimen type (sensitivity 98-100%).[13,61-63] FVU has been shown to be more sensitive than urethral swabs.[13,61,64]

There is sparse and conflicting data for meatal swabs; in one study, self-taken penile meatal swabs compared with urethral swabs had a sensitivity of 79% for *M. genitalium*, whereas in the same study the sensitivity for detection of *C. trachomatis* was 98%.[65] Another study detected more infections using self-taken meatal swabs than FVU (15.3% vs 12.6%).[66]

5.2.2 Women

Most studies suggest that in women, vulvovaginal swabs are the most sensitive specimen, followed by endocervical swabs.[61,67-69] Using both vaginal and endocervical swabs increases the sensitivity further (sensitivity using a PCR assay: vaginal 85.7%, endocervical 74.3%, combined 95.7%).[68] In one study, a quarter of infections would have been missed by only testing one specimen.[67] A recent study using a more sensitive assay[61] suggests that a vaginal swab alone is sufficient (sensitivity of vaginal swab 100%, endocervical swab 95.6%).

In the majority of published studies, FVU in cisgender women was found to be less sensitive than vaginal or endocervical swabs (FVU sensitivity 58 – 71%).[13,68,69] However a few small studies have

found no significant difference in the sensitivity between specimen types,[62] or FVU to be superior to vaginal swabs.[64,70]

5.2.3 Considerations for people following gender reassignment surgery (GRS)

There are a paucity of data concerning *M. genitalium* infection in individuals following GRS. It is therefore difficult to recommend an optimal specimen type but this should be guided by sexual history and symptoms. For more detail, clinicians should refer to the forthcoming BASHH standards for trans and non-binary people document.

5.2 Recommendations:

- We recommend first void urine as the specimen of choice in cisgender men (1C)
- We recommend vaginal swabs (clinician- or self-taken) as the specimen of choice in cisgender women (1C)
- We recommend that where possible, all *M. genitalium*-positive specimens should be tested for macrolide resistance mediating mutations (1B)

5.3 Window period:

There are no data on the incubation period for *M. genitalium,* or on the likely window period before a laboratory test becomes reliably positive. However, it is likely that sensitive tests will detect early infection.

6. Management

6.1 General advice

Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced with clear and accurate written information. A patient information leaflet for *M. genitalium* can be found on the guidelines page of the BASHH website. This will be updated when new guidance is published or new information becomes available.

Patients should be advised to abstain from sexual intercourse until 14 days after the start of treatment, and until symptoms have resolved. Where azithromycin has been used this is especially important because of its long half-life, and is likely to reduce the risk of selecting/inducing macrolide resistance if the patient is re-exposed to *M. genitalium*. We recommend a test of cure (TOC) should be performed in all patients.

6.2 Treatment of uncomplicated urogenital infection (urethritis, cervicitis)

6.2.1 Eradication rates of *M. genitalium* following treatment with macrolides are decreasing globally and rates of resistance are 30-100%.[71] Macrolide resistance in the UK is estimated at around 40% although data are lacking.[68] Reference laboratory data show higher rates of resistance but are biased as isolates tend to come from patients who have previously failed treatment.[69]

Despite this *M. genitalium* still responds to azithromycin in the majority of cases. This has previously been given as 500mg single dose followed by 250mg once daily for 4 days, although the evidence that this regimen is less likely to select for macrolide resistance than 1g as a single dose is conflicting.[27] More recently, data from Australia using a total of 2.5g azithromycin over 4 days showed much lower rates of treatment failure in combination with resistance-guided management.[72] Although never evaluated, using a 2g dose over 3 days (1g followed by 500mg for 2 days) may improve microbiological cure rates and reduce the risk of macrolide resistance developing in *M. genitalium*, whilst being tolerable.[57]

Knowledge of macrolide resistance status is important in determining whether azithromycin should be given but will depend on such testing being available. Even where an organism is known to be initially macrolide-sensitive, an azithromycin-regimen should not be repeated following treatment failure because it is likely that resistance has developed on treatment.

6.2.2 Although doxycycline as monotherapy has poor efficacy and eradication rates are low at about 30-40%, there is evidence that prior treatment with doxycycline may improve treatment success when given with, or followed by an extended azithromycin regimen.[27,72] This is biologically plausible as doxycycline reduces the organism load and hence the risk of pre-existing macrolide mutations

being present. However evidence for this approach is limited, and clinicians should collate and share evidence to inform the utility of this practice.

6.2.3 Moxifloxacin still has excellent efficacy in Europe[54,73] although resistance is increasing in Asia-Pacific where its use is greater.[74] Using moxifloxacin first line in all cases of *M. genitalium* is not recommended because future therapeutic options are limited. Regarding optimal duration of therapy, a recent meta-analysis reported no significant difference in 7- and 10-day regimens, although more treatment failures were seen in the 7-day regimens. Thus, 10 days is preferred.[75]

See Fig. 1 for suggested treatment pathway for men presenting with NGU who subsequently test positive for *M. genitalium.*

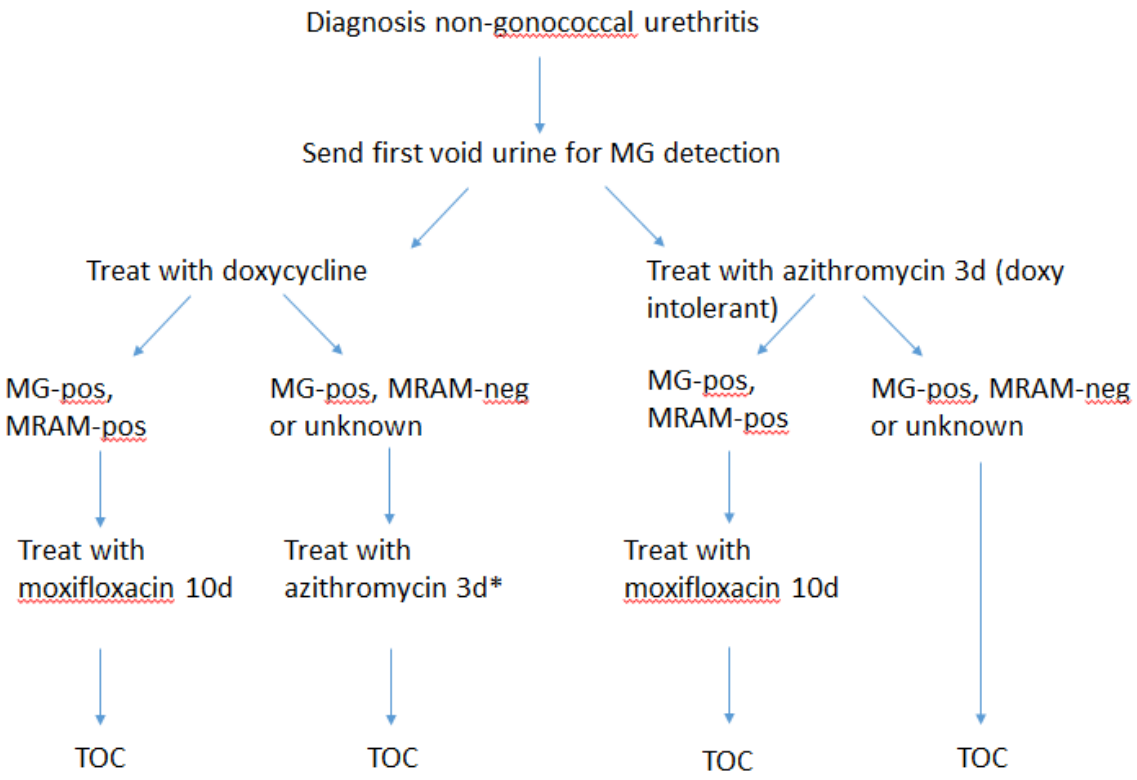

Fig. 1 Suggested treatment pathway for men presenting with non-gonococcal urethritis who subsequently test positive for *M. genitalium*

MG = *Mycoplasma genitalium*; Doxycycline 7d = doxycycline 100mg bd for 7 days; Azith 3d – azithromycin 1g, then 500mg od for 2 days; Moxifloxacin 10d = moxifloxacin 400mg od for 10 days; MRAM = macrolide resistance associated mutation; TOC = test of cure

*Azithromycin 3d should be started within 2 weeks of finishing doxycycline

6.2.4 Recommended regimens (uncomplicated infections):

- Doxycycline 100mg bd for seven days followed by azithromycin 1g orally as a single dose then 500mg orally once daily for 2 days* where organism is known to be macrolide-sensitive or where resistance status is unknown (1D)
- Moxifloxacin 400mg orally once daily for 10 days if organism known to be macrolide-resistant or where treatment with azithromycin has failed** (1B)

* Given that most individuals will have had doxycycline as first-line treatment for uncomplicated infection, a repeat course is unnecessary once the *M. genitalium* positive result is known. Azithromycin should be given immediately after doxycycline, and ideally within 2 weeks of completing doxycycline. If this is not possible, the course of doxycycline should be repeated prior to giving azithromycin.

**Treatment failure is defined as persistent symptoms following treatment, or a positive test of cure taken five weeks post-treatment

6.3 Treatment of complicated urogenital infection (PID, epididymo-orchitis)

6.3.1 There are few studies examining the efficacy of extended azithromycin regimens in the treatment of PID and epididymo-orchitis caused by *M. genitalium*. Data from a recent PID RCT showed high rates of macrolide resistance mutations in specimens positive for *M. genitalium.*[76] Given the need for prompt and effective treatment in complex STI syndromes, patients with confirmed *M. genitalium* infection, or who have a partner who has tested positive for *M. genitalium* should be given moxifloxacin as a 14-day regimen.[75]

6.3.2 Recommended regimens (complicated infection):

- Moxifloxacin 400mg orally once daily for 14 days (1D)

6.4 Partner notification

Only current partner(s) (including non-regular partners where there is likely to be further sexual contact) should be tested and treated if positive. This is to reduce the risk of re-infection to the index patient. Partners should be given the same antibiotic as the index patient unless there is available resistance information to suggest otherwise.

6.5 Alternative regimens

Very little evidence exists for the effectiveness of the following regimens but they may be considered:

- Doxycycline 100mg bd for seven days* then pristinamycin 1g orally four times daily for 10 days[77]
- Pristinamycin 1g orally four times daily for 10 days[77]
- Doxycycline 100mg orally twice daily for 14 days[78,79]
- Minocycline 100mg orally twice daily for 14 days[80,81]

* Prior treatment with doxycycline will reduce *M. genitalium* load and has been demonstrated to be of benefit if administered prior to extended azithromycin and also pristinamycin treatment which is only 75% effective as mono-therapy.[27]

6.6 Rectal infection

This should be managed in the same way as urogenital infection. For severe proctitis, a longer course of moxifloxacin (14 days) may be considered.

6.7 Sourcing of unlicensed products

Pristinamycin is not currently available in the UK and must be imported against a prescription. The cost of importing medicines can be high and availability is inconsistent. An MHRA register of licensed wholesalers who can import medicines without a UK Marketing Authorisation is available at: https://www.gov.uk/government/publications/human-and-vetinary-medicines-register-of-licensed-wholesale-distribution-sites-december-2014. At the time of writing, pristinamycin was available from several wholesalers with a lead time of two to three weeks.

6.8 Pregnancy and breastfeeding

6.8.1 Pregnancy

Data on *M. genitalium* and its association with adverse pregnancy outcomes are limited, however it has been associated with a small increased risk of preterm delivery and spontaneous abortion.[42,46,82 83] Azithromycin use during pregnancy is unlikely to increase the risk of birth defects or adverse pregnancy outcomes.[84-86] A three-day course of azithromycin can be used for uncomplicated *M. genitalium* infection detected in pregnancy. The use of moxifloxacin in pregnancy is contra-indicated. In women with likely macrolide resistance, or with upper genital tract infection in pregnancy, options are limited.[87-89] Although doxycycline is considered safe for use in the first trimester by the FDA, the BNF advises against its use in all trimesters. There are no data regarding the use of pristinamycin in pregnancy. An informed discussion should be had with the pregnant woman around the risks associated with the use of these medicines in pregnancy and the risks of adverse outcomes associated with *M. genitalium* infection, and where possible treatment should be delayed until after pregnancy.

6.8.2 Breastfeeding

Very low levels of azithromycin are detected in breast milk, and systemic exposure in infants does not exceed that observed when azithromycin is administered for treatment, therefore risk is considered to be low.[90] Infants should be monitored for possible side effects due to effects on the gastrointestinal flora including diarrhoea and candidiasis. A large cohort study found a significantly increased risk of pyloric stenosis in breastfed infants with maternal use of macrolides between 0 to 13 days of delivery.[91] Doxycycline is excreted into breast milk and is contraindicated in nursing mothers due to the risk of tooth discolouration and effects on bone growth. Use of moxifloxacin is contra-indicated during breastfeeding. Pristinamycin is contraindicated during breastfeeding due to its side effect profile.[92]

6.9 Adverse events

Azithromycin, doxycycline, moxifloxacin and pristinamycin can all cause gastro-intestinal problems including nausea but symptoms are most frequently reported with doxycycline and azithromycin doses over 1g. Caution should be taken when prescribing azithromycin or moxifloxacin to patients already on medications which may prolong the QT interval. The European Medicines Agency committee has recommended that the use of fluoroquinolone antibiotics should be restricted following a review of their disabling and potentially long-lasting side effects.[93] Healthcare professionals should advise patients to stop treatment with a fluoroquinolone antibiotic at the first sign of side effects involving muscles, tendons, bones or the nervous system. The only absolute contra-indication to moxifloxacin is known hypersensitivity to this class of drugs. Hepatotoxicity has been reported but is very rare (<1/10 000).

6.10 HIV

Treatment of *M. genitalium* in HIV-positive individuals is the same as that for HIV-negative individuals.

6.11 Test of Cure and follow up

TOC is vital in ensuring microbiological clearance of infection and is recommended for all patients with confirmed *M. genitalium*, even if the infection was initially sensitive to macrolides, to detect resistance which may have emerged following treatment. Persistence of *M. genitalium* has been demonstrated in the absence of symptoms in men treated for NGU.[94,95] This occurs in about 10-20% of men treated with doxycycline, but is not associated with development of AMR.[27,95] Persistence of *M. genitalium* following treatment with azithromycin and moxifloxacin is strongly associated with antimicrobial resistance.[94,95]

The optimal time to TOC has not been determined, but recent data suggest that very early testing after treatment when DNA load is low can give false negative results.[96] Clinical cure (i.e. resolution of symptoms) should be established at the TOC visit. The risk of re-infection should be excluded and compliance with medication should be verified.

- We recommend all patients should attend for a TOC five weeks (and no sooner than three weeks in order to avoid false negative results) after the start of treatment to ensure microbiological cure and to help identify emerging resistance (1D)

Treatment failures should be reported to PHE at: https://hivstiwebportal.phe.org.uk

7. Auditable Outcome Measures

New cases of *M. genitalium* should have SHHAPT (Sexual Health and HIV Activity Property Type) code "C16" submitted to GUMCAD (performance standard 97%)

Individuals treated for *M. genitalium* should have a TOC at least 5 weeks after the start of treatment (performance standard 97%)

Cases of confirmed treatment failure by positive TOC should be reported to PHE at: https://hivstiwebportal.phe.org.uk

Individuals should be provided with written information about their diagnosis and management (performance standard 97%)

PN should be performed and documented according to the BASHH statement on PN for sexually transmissible infections (performance standard 97%)

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Appendix 1: Example of PICO question used and list of all PICO questions

What are the optimal specimen types for testing for *M. genitalium* in men and women?

	INCLUSION	EXCLUSION
Period of publication	Jan 2010 – Jun 2017	
Study design / type	Meta-analysis or systematic review Randomised controlled trials (RCTs) Non-randomised, prospective comparative studies Prospective observational studies (e.g. cohort studies) Laboratory studies	Non-pertinent publication types (e.g. expert opinions, letters to the editor, editorials (unless include original data), comments, not referring to *M. genitalium*)
Study quality	Study duration (no minimum) Number of subjects (no minimum)	
Study population	Adults (aged >15 years or above) in Europe, N America, Australasia	Children (≤15 years) Adults (aged >15 years or above) outside Europe, N America, Australasia
Study comparison	Not applicable	
Specific outcomes of interest	Sensitivity/specificity Inhibitory results Ability to test for other STIs concurrently	No exclusions based on outcome measures

PICO questions used:

(1) What is the prevalence of asymptomatic *M. genitalium* in the following populations?

Heterosexual men

Heterosexual women

MSM: HIV-negative

MSM: HIV-positive

Pregnant women

(2) What is the prevalence of symptomatic *M. genitalium* in the following clinical presentations?

Non-gonococcal urethritis / non-specific urethritis (first presentation)

Non-gonococcal urethritis / non-specific urethritis (persistent and recurrent episodes)

Muco-purulent cervicitis / intermenstrual bleeding / post-coital bleeding

Pelvic inflammatory disease / salpingitis

Proctitis

Vaginal discharge

(3) What are the clinical features of *M. genitalium* infection?

(4) What evidence is there to support testing for *M. genitalium* infection in the populations and clinical scenarios examined above?

(5) What are the optimal specimen types for testing for *M. genitalium* in men and women?

(6) What is the incubation/window period for *M. genitalium* detection?

(7) What assays are available for the detection of *M. genitalium*?

(8) What are the rates of microbiological cure/clearance rate/clinical cure/treatment failure for each of the following antimicrobial regimens?

Azithromycin (all regimens)

Moxifloxacin

Other quinolones

Tetracyclines (inc. doxycycline)

Pristinamycin

Other macrolides

(9) What are the pharmacological characteristics of the following antimicrobials in the context of treatment of *M. genitalium*?

Azithromycin (all regimens)

Moxifloxacin

Other quinolones

Tetracyclines (inc. doxycycline)

Pristinamycin

Other macrolides

(10) Is a test of cure required, and if so, what is the optimal time to conduct a test-of-cure following treatment?

(11) How should the partners of patients with *M. genitalium* infection be managed?

Appendix 2: NICE Equality Impact Assessment

Were any potential equality issues with respect to age, disability, gender, race, pregnancy and sexual orientation been identified before or during consultation, and, if so what are they?

The guideline is intended for the treatment of individuals aged 16 years and older. *M. genitalium* is more common in men and women of black ethnicity but this has not influenced the recommendations for testing. The patient information leaflet (PIL) is written in English and was piloted in English-speaking patients only. No issues were raised with respect to disability, gender, pregnancy and sexual orientation. Care has been taken to include the correct anatomical site-specific terminology rather than gender terminology for specimen taking and there is a separate section for management of *M. genitalium* in pregnancy

Have any changes to the scope been made as a result of consultation to highlight potential equality issues?

No

Is the primary focus of the guideline a population with a specific disability- related communication need?

No