

1 2018 BASHH UK national guideline for the 2 management of infection with *Mycoplasma genitalium*

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4 Suneeta Soni, Paddy Horner, Michael Rayment, Nicolas Pinto-Sander, Nadia Naous, Andy Parkhouse,
5 Darren Bancroft, Carl Patterson, Helen Fifer

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9 **Introduction**

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

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

19

20 **Editorial independence**

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

23

24

25 **Conflict of interest**

26 All authors have signed BASHH CEG CoI forms. PH is partially funded by the National Institute for
27 Health Research Health Protection Research Unit (NIHR HPRU) in Evaluation of Interventions at the
28 University of Bristol. HF is employed by Public Health England (PHE); PHE offers Mycoplasma

1 genitalium testing for a fee, and has received remuneration for contract research of diagnostic
2 assays and consultancy work. None of the other authors have any declarations. The views expressed
3 by the authors are not necessarily those of the NHS, the NIHR, PHE or the Department of Health.

4

5 **Rigour of development**

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

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10

11 **Search strategy**

12 The writing group determined PICO (**P**atient, **I**ntervention, **C**omparison, **O**utcome) questions which
13 formed the basis for the literature search, and are listed in *Appendix 1*.

14 A search was conducted using Medline, Embase, the Cochrane library and NHS Evidence. The search
15 heading was kept broad ("genitalium") to include all the guideline questions. Only publications in the
16 English language were considered. Age, country and study design limits were included in the PICO
17 criteria, except that studies from Japan were considered for questions 8, 9 and 10 because it was felt
18 that evidence in these studies, particularly with respect to resistance and treatment issues, would
19 contribute significantly to and inform the guideline. (see *Appendix 1*) . 'Grey literature' included
20 conference abstracts from IUSTI, BASHH, BHIVA, ICAAC, ASHM, ECCMID in last 3 years. The writing
21 group used a modified GRADE system for assessing evidence and formulate recommendations.

22

23

24 **Equality impact assessment** – to be completed after first consultation

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28 **Stakeholder involvement, piloting and feedback.**

29 The draft guideline recommendations were presented at the joint British HIV Association and BASHH
30 annual conference 2018. The draft guideline was appraised by the CEG using the AGREE instrument,
31 posted on the BASHH website for a consultation period of 3 months and piloted in a sample of
32 clinics. In response to the consultation, suitable amendments were made to the guideline and the

1 final draft was submitted to the CEG. (appendix XX—to be added post-consultation). The patient
2 information leaflet (PIL) was reviewed by the CEG, BASHH patient and public panel and also piloted
3 in a sample of clinics and comments were reviewed and incorporated where appropriate.

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

7 The guideline will be updated every 5 years according to the BASHH CEG guideline framework. This
8 interval could be shorter should new data arise which could significantly impact recommendations.

9

10 **Patient and Public Involvement**

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

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1 Summary of Recommendations

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

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3

1 **Introduction**

2

3 **1. Microbiology**

4

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

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

20

1 **2. Epidemiology**

2

3 **2.1 Prevalence in general population, and risk factors for infection**

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

10

11 **2.2 Sexual transmission**

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

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

22

23

24 **2.3 Co-infection with other STIs**

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

29

1 **2.4 Clinical Associations**

2

3 **2.4.1 Non-gonococcal urethritis**

4 *M. genitalium* infection is unequivocally and strongly associated with NGU. Typically, the prevalence
5 of *M. genitalium* in men with NGU is 10-20% and in male patients with non-chlamydial non-
6 gonococcal urethritis (NCNGU) is 10-35% [3], as compared to 1-2% in the general population[11, 35].
7 In one meta-analysis of 19 observational studies examining *M. genitalium* infection with molecular
8 techniques, 436/2069 patients with NGU (21.1%) were positive for *M. genitalium* versus 121/1810
9 controls (6.7%), yielding a pooled odds ratio of 3.8 [95% CI 3.0-4.9][13]. Further systematic reviews
10 have demonstrated a similar association, and demonstrated a yet stronger strength of association
11 with non-chlamydial non-gonococcal urethritis (NCNGU)[3]. *M. genitalium* is also associated with
12 persistent and recurrent urethritis, where up to 40% of patients may have *M. genitalium*
13 detected[36]. A recent meta-analysis demonstrated an odds ratio of 26 for *M. genitalium* detection
14 in men with persistent urethritis[37].

15

16 **2.4.2 *M. genitalium* in the female reproductive tract**

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

19

20 A recent meta-analysis has demonstrated significant associations between *M. genitalium* and
21 cervicitis (pooled OR 1.66) and PID (pooled OR 2.14), in addition to pre-term birth and spontaneous
22 abortion (pooled ORs 1.89 and 1.82 respectively)[42]. *M. genitalium* is likely to be linked
23 aetiologically to PID. It has been shown to ascend from the lower to upper female genital tract[3] ,
24 has been detected frequently from endometrial biopsies in women with PID [43] and can cause
25 epithelial ciliary damage in human fallopian tube culture. However an association with tubal factor
26 infertility has not yet been demonstrated and conducting studies to determine this will be difficult
27 [3, 8, 44].

28

29

30

1 **2.4.3 Asymptomatic infection**

2 The evidence suggests that the majority of people infected with *M. genitalium* in the genital tract do
3 not develop disease [27, 45]. Current treatments are imperfect and associated with development of
4 antimicrobial resistance[46, 47]. There is no evidence that screening asymptomatic individuals will
5 be of benefit, and indeed is likely to do harm at a population level [48].

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

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1 **3. Clinical Features**

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3 3.1 Signs and symptoms in males [3]:

4 None – the majority are asymptomatic [27]

5 Urethral discharge

6 Dysuria

7 Penile irritation

8

9 Urethral discomfort

10

11 Urethritis (acute, persistent, recurrent)

12 Balanoposthitis (in one study)[49]

13

14 3.2 Complications in males

15 Sexually acquired reactive arthritis (SARA) may occur

16 Epididymitis

17

18 The clinical presentation of *M. genitalium* urethritis is similar to other causes and thus clinical
19 features of acute symptomatic NGU cannot be used to determine the infective aetiology[17, 27, 50-
20 53]. Although the proportion of infected men that develop symptoms is unknown this is likely to be
21 <10%[27].

22

23 Urethral discharge may be present spontaneously or on expression, and urethritis is confirmed by
24 demonstrating five or more PMNLs per high power (x1000) microscopic field (averaged over five
25 fields with the greatest concentration of PMNLs) on a smear obtained from the anterior urethra [54].

26 It is possible that sexually acquired reactive arthritis may occur as a result of *M. genitalium*
27 infection[3, 27, 55]. An association with epididymitis is possible, but current data are lacking to
28 support an association with prostatitis[3]. *M. genitalium* has been demonstrated at high prevalence

1 in rectal samples from men who have sex with men (MSM) (particularly HIV-positive MSM), and one
2 study suggesting a potential association showed that men with symptoms of proctitis had higher
3 bacterial load of *M. genitalium* than those without rectal symptoms [5, 23]. This warrants further
4 investigation with larger studies.

5

6 3.3 Signs and symptoms in females

7 Asymptomatic (majority)[18, 40]

8 Dysuria

9 Post-coital bleeding

10 Painful inter-menstrual bleeding

11 Cervicitis

12 Lower abdominal pain (see Complications: PID)

13

14 3.4 Complications in females

15 Pelvic inflammatory disease

16 Tubal factor infertility (uncertain association)

17 SARA

18 Pre-term delivery

19

20 Individuals with cervicitis due to *M. genitalium* frequently have no symptoms at all. If present,
21 symptoms are nonspecific, with the most common symptom being post-coital bleeding [56].

22 Examination is frequently normal, but on speculum examination the presence of mucopurulent
23 cervical discharge, cervical friability and elevated numbers of poly-morphonuclear leukocytes cells
24 on cervical sample Gram staining are suggestive of infection[18, 38, 40, 57].

25 Clinical signs and symptoms of *M. genitalium*-associated pelvic inflammatory disease (PID) are
26 similar to, and indistinguishable from, PID due to *C. trachomatis*.

1 **4. Recommendations for testing**

2

3 4.1 Based on symptoms

4 We recommend testing for *M. genitalium* infection in people with non-gonococcal urethritis (Grade
5 1B)

6 We recommend testing for *M. genitalium* infection in people with signs and symptoms suggestive of
7 pelvic inflammatory disease (Grade 1B)

8 Consider testing for *M. genitalium* infection in people with signs or symptoms of muco-purulent
9 cervicitis, particularly post-coital bleeding (Grade 2B)

10 Consider testing for *M. genitalium* infection in people with epididymitis (Grade 2D)

11 Consider testing for *M. genitalium* infection in people with sexually-acquired proctitis (Grade 2D)

12

13 4.2 Based on risk factors

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

15 There are currently insufficient data to recommend routine screening for *M. genitalium* infection in
16 asymptomatic individuals

17 Asymptomatic individuals with confirmed chlamydia and/or gonorrhoea infection should not be
18 routinely tested for *M. genitalium*.

19

1 **5. Diagnosis**

2 *M. genitalium* has fastidious nutritional requirements and is extremely slow growing, therefore
3 culture is not appropriate for diagnosis. Nucleic acid amplification tests (NAATs) that detect *M.*
4 *genitalium* specific DNA or RNA in clinical specimens are the only useful diagnostic method. Several
5 CE marked commercial tests are available, although none are currently FDA approved. Careful
6 consideration of assay performance based on published data is essential, as the different NAATs are
7 likely to have varying performance and lack extensive validation[58]. Local validation is required
8 before the implementation of any test.

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

16 17 **5.1 Specimen collection**

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

21 **5.1.1 Men**

22 First void urine (FVU) is the most sensitive specimen type (sensitivity 98-100%) [13, 58, 59]Tabrizi
23 2016(18). FVU has been shown to be more sensitive than urethral swabs [13, 58, 60]

24 There is sparse and conflicting data for meatal swabs; in one study, self-taken penile meatal swabs
25 compared with urethral swabs had a sensitivity of 79% for *M genitalium*, whereas in the same study
26 the sensitivity for detection of *C. trachomatis* was 98% [61]. Another study detected more infections
27 using self-taken meatal swabs than FVU (15.3% vs 12.6%)[62] .

28 **5.2.2 Women**

29 Most studies suggest that in women, vulvovaginal swabs are the most sensitive specimen, followed
30 by endocervical swabs [58, 63-65]. Using both vaginal and endocervical swabs increases the

1 sensitivity further (sensitivity using a PCR assay: vaginal 85.7%, endocervical 74.3%, combined
2 95.7%)[64] . In one study, a quarter of infections would have been missed by only testing one
3 specimen [63]. A recent study using a more sensitive assay[58] suggests that a vaginal swab alone is
4 sufficient (sensitivity of vaginal swab 100%, endocervical swab 95.6%).

5 In the majority of published studies, FVU in cisgender women was found to be less sensitive than
6 vaginal or endocervical swabs (FVU sensitivity 58 – 71%) [13, 64, 65] . However a few small studies
7 have found no significant difference in the sensitivity between specimen types [59], or FVU to be
8 superior to vaginal swabs [60, 66]

9 5.2.3 Considerations for transgender men and non-binary (AFAB) people following gender
10 reassignment surgery (GRS)

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

15

16 **5.2 Recommendations:**

17 We recommend first void urine as the specimen of choice in cisgender men (1C)

18 We recommend vaginal swabs (clinician- or self-taken) as the specimen choice in cisgender women
19 (1C)

20 We recommend that where possible, all *M. genitalium*-positive specimens should be tested for
21 macrolide resistance mediating mutations (1B)

22

23 **5.3 Window period:**

24 There are no data on the incubation period for *M genitalium*, nor on the likely window period before
25 a laboratory test becomes reliably positive. However, it is likely that sensitive tests will detect early
26 infection.

27

28

1 **6. Management**

2 **6.1 General advice**

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

8 Patients should be advised to abstain from sexual intercourse until they and their partner(s) have
9 completed treatment or, in patients with PID, until 14 days after the start of treatment, and until
10 symptoms have resolved. We recommend a test of cure (TOC) should be performed in all patients.

11 12 **6.2 Treatment of uncomplicated urogenital infection (urethritis, cervicitis)**

13 6.2.1 Eradication rates of *M. genitalium* following treatment with macrolides are decreasing globally
14 and rates of resistance are 30-100%[67]. Macrolide resistance in UK is estimated at around 40%
15 although data are lacking and biased in that reference laboratory isolates come from patients who
16 have previously failed treatment [68, 69].

17
18 Despite this *M. genitalium* still responds to azithromycin in the majority of cases. This has previously
19 been given as 500mg single dose followed by 250mg od for 4 days although the evidence that this
20 regimen is less likely to select for macrolide resistance than 1g as a single dose is conflicting [27].
21 More recently, data from Australia using a total of 2.5g azithromycin over 4 days showed much
22 lower rates of treatment failure in combination with resistance-guided management[70]. Although
23 never evaluated, using a 2 g dose over 3 days (1g followed y 500mg for 2 days) may improve
24 microbiological cure rates and reduce the risk of macrolide resistance developing in *M. genitalium*
25 whilst being tolerable.[54]

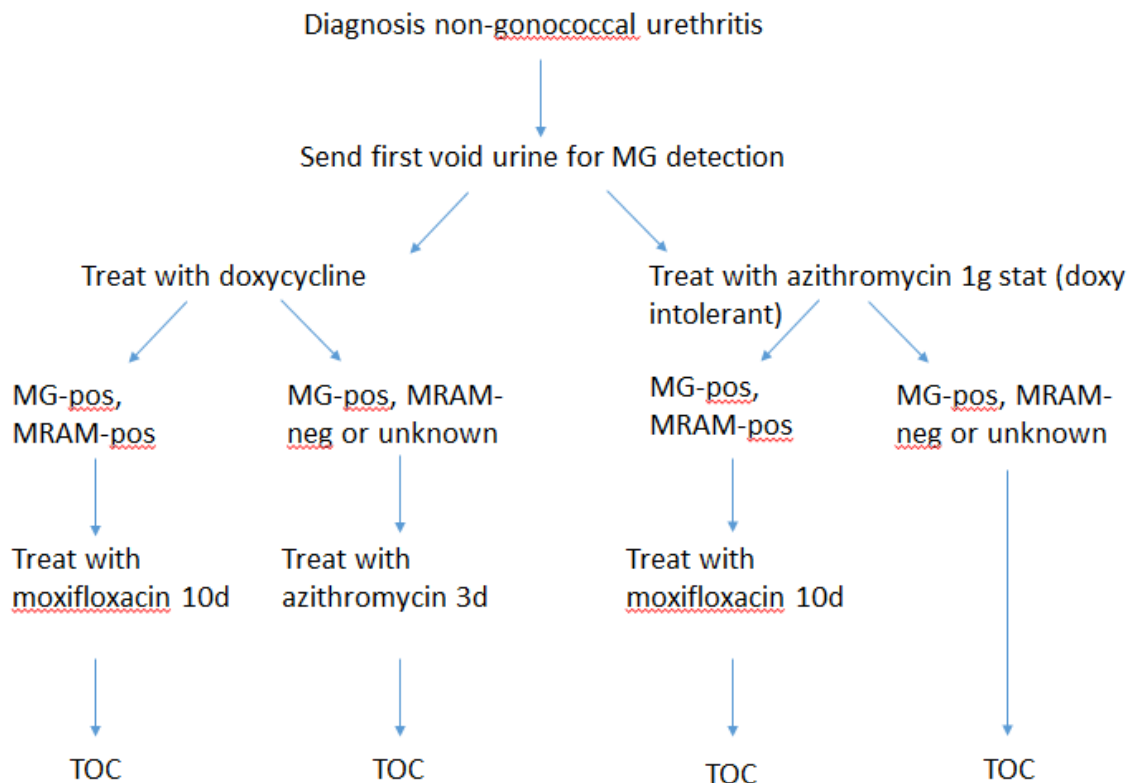
26
27 Knowledge of macrolide resistance status is important in determining whether azithromycin should
28 be given but will depend on such testing being available. Even where an organism is known to be
29 initially macrolide-sensitive, an azithromycin-regimen should not be repeated following treatment
30 failure because of the likelihood of developing subsequent resistance.

31

1 6.2.2 Although doxycycline as monotherapy has poor efficacy and eradication rates are low at about
 2 30-40%, there is evidence that prior treatment with doxycycline may improve treatment success
 3 when given with, or followed by an extended azithromycin regimen [27, 70]. This is biologically
 4 plausible as doxycycline reduces the organism load and hence the risk of pre-existing macrolide
 5 mutations being present. However evidence for this approach is limited, and clinicians should collate
 6 and share evidence to inform the utility of this practice.

7 6.2.3 Moxifloxacin still has excellent efficacy in Europe[51, 71]although resistance is increasing in
 8 Asia-Pacific where its use is greater[72] . Using moxifloxacin first line in all cases of *M. genitalium* is
 9 not recommended because future therapeutic options are limited. Regarding optimal duration of
 10 therapy, a recent meta-analysis reported no significant difference in 7- and 10-day regimens,
 11 although more treatment failures were seen in the 7-day regimens. Thus, 10 days is preferred[73].

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



14

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

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

1 **6.2.4 Recommended regimens (uncomplicated infections):**

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

8 * Given that most individuals will have had doxycycline as first-line treatment for uncomplicated
9 infection, a repeat course is unnecessary once the *M. genitalium* positive result is known.
10 Azithromycin should ideally be given immediately after doxycycline but the time interval between
11 the two regimens will depend on the time to results which varies between clinics.

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

14

15 **6.3 Treatment of complicated urogenital infection (PID, epididymo-orchitis)**

16 6.3.1 There are few studies examining the efficacy of extended azithromycin regimens in the
17 treatment of PID and epididymo-orchitis caused by *M. genitalium*. Data from a recent PID RCT
18 showed high rates of macrolide resistance mutations in specimens positive for *M. genitalium* [74].
19 Given the need for prompt and effective treatment in complex STI syndromes, patients with
20 confirmed *M. genitalium* infection, or who have a partner who has tested positive for *M. genitalium*
21 should be given moxifloxacin as a 14-day regimen[73].

22

23 **6.3.2 Recommended regimens (complicated infection):**

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

25

26 **6.4 Partner notification**

27 Only current partner(s) (including non-regular partners where there is likely to be further sexual
28 contact) should be tested and treated. This is primarily to reduce the risk of re-infection to the index

1 patient. Partners should be given the same antibiotic as the index patient unless there is available
2 resistance information to suggest otherwise.

3

4 **6.5 Alternative regimens**

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

7 1) Doxycycline 100mgs bd for seven days* then pristinamycin 1g orally four times daily for
8 10 days [75]

9 2) Pristinamycin 1g orally four times daily for 10 days[75]

10 3) Doxycycline 100mg orally twice daily for 14 days [76, 77]

11 4) Minocycline 100mg orally twice daily for 14 days [78, 79]

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

15

16 **6.6 Rectal infection**

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

19

20 **6.7 Sourcing of unlicensed products**

21 Pristinamycin is not currently available in the UK and must be imported against a prescription. The
22 cost of importing drugs can be high and availability is inconsistent. An MHRA register of licensed
23 wholesalers who can import drugs without a UK Marketing Authorisation is available at:

24 [https://www.gov.uk/government/publications/human-and-veterinary-medicines-register-of-licensed-
25 wholesale-distribution-sites-december-2014](https://www.gov.uk/government/publications/human-and-veterinary-medicines-register-of-licensed-
25 wholesale-distribution-sites-december-2014). At the time of writing, pristinamycin was available

26 from several wholesalers with a lead time of two to three weeks.

27

1 **6.8 Pregnancy and breastfeeding**

2 6.8.1 Pregnancy

3 Data on *M. genitalium* and its association with adverse pregnancy outcomes are limited, however it
4 has been associated with a small increased risk of preterm delivery and spontaneous abortion [42,
5 44, 80, 81]. Azithromycin use during pregnancy is unlikely to increase the risk of birth defects or
6 adverse pregnancy outcomes [82-84]. A 3-day course of azithromycin can be used for
7 uncomplicated *M. genitalium* infection detected in pregnancy. The use of moxifloxacin in pregnancy
8 is contra-indicated. In women with likely macrolide resistance, or with upper genital tract infection
9 in pregnancy, options are limited. Doxycycline is considered safe for use in the first trimester by the
10 FDA and may be used. There are no data regarding the use of pristinamycin in pregnancy. An
11 informed discussion should be had with the pregnant woman around the risks associated with the
12 use of these drugs in pregnancy and the risks of adverse outcomes associated with *M. genitalium*
13 infection, and where possible treatment should be delayed until after pregnancy.

14

15 6.8.2 Breast feeding

16 Very low levels of azithromycin are detected in breast milk, and systemic exposure in infants does
17 not exceed those observed when that azithromycin is administered for treatment, therefore risk is
18 considered to be low [85]. Infants should be monitored for possible side effects due to effects on the
19 gastrointestinal flora including diarrhoea and candidiasis. A large cohort study found a significantly
20 increased risk of pyloric stenosis in breastfed infants with maternal use of macrolides between 0 to
21 13 days of delivery [86]. Doxycycline is excreted into breast milk and is contraindicated in nursing
22 mothers due to the risk of tooth discolouration and effects on bone growth. Use of moxifloxacin is
23 contra-indicated during breastfeeding. Pristinamycin is contraindicated during breastfeeding due to
24 its side effect profile [87].

25

26 **6.9 Adverse events**

27 Azithromycin, doxycycline, moxifloxacin and pristinamycin can all cause gastro-intestinal problems
28 including nausea but symptoms are most frequently reported with doxycycline and azithromycin
29 doses over 1g. The only absolute contra-indication to moxifloxacin is known hypersensitivity to this
30 class of drugs. Hepatotoxicity has been reported as has tendon rupture, but both are very rare
31 (<1/10 000).

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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

The optimal time to test of cure has not been determined, but recent data suggest that very early testing after treatment when DNA load is low can give false negative results [88]. 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) 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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22

23

1 **Appendix 1: Example of PICO question used**

2 What are the optimal specimen types for testing for MG in men and women?

	INCLUSION	EXCLUSION
Period of publication	Jan 2010 – Jun 2017	
Study design / type	<ul style="list-style-type: none"> • Meta-analysis or systematic review • Randomised controlled trials (RCTs) • Non-randomised, prospective comparative studies • Prospective observational studies (e.g. cohort studies) • Laboratory studies 	<ul style="list-style-type: none"> • Non-pertinent publication types (e.g. expert opinions, letters to the editor, editorials (unless include original data), comments, not referring to MG)
Study quality	<ul style="list-style-type: none"> • Study duration (no minimum) • Number of subjects (no minimum) 	
Study population	<ul style="list-style-type: none"> • Adults (aged >15 years or above) in Europe, N America, Australasia 	<ul style="list-style-type: none"> • Children (≤15 years) • Adults (aged >15 years or above) outside Europe, N America, Australasia
Study comparison	<ul style="list-style-type: none"> • Not applicable 	
Specific outcomes of interest	<ul style="list-style-type: none"> • Sensitivity/specificity • Inhibitory results • Ability to test for other STIs concurrently 	<ul style="list-style-type: none"> • No exclusions based on outcome measures

3

4

5 PICO Questions used

- 1 1. What is the prevalence of **asymptomatic** MG in the following populations?
- 2 • Heterosexual men
- 3 • Heterosexual women
- 4 • MSM – HIV negative
- 5 • MSM – HIV positive
- 6 • Pregnant women
- 7
- 8 2. What is the prevalence of **symptomatic** MG in the following clinical presentations?
- 9 • Non-gonococcal urethritis / non-specific urethritis (first presentation)
- 10 • Non-gonococcal urethritis / non-specific urethritis (persistent and recurrent
- 11 episodes)
- 12 • Muco-purulent cervicitis / intermenstrual bleeding / post-coital bleeding
- 13 • Pelvic inflammatory disease / salpingitis
- 14 • Proctitis
- 15 • Vaginal discharge
- 16 3. What are the clinical features of MG infection
- 17 4. What evidence is there to support testing for MG infection in the populations and clinical
- 18 scenarios examined above?
- 19 5. What are the optimal specimen types for testing for MG in men and women?
- 20 6. What is the incubation/window period for MG detection?
- 21 7. What assays are available for the detection of MG?
- 22 8. What are the rates of microbiological cure/clearance rate/clinical cure/treatment failure for
- 23 each of the following antimicrobial regimens?
- 24 • Azithromycin (all regimens)
- 25 • Moxifloxacin
- 26 • Other quinolones
- 27 • Tetracyclines (inc. doxycycline)
- 28 • Pristinamycin
- 29 • Other macrolides
- 30 9. What are the pharmacological characteristics of the following antimicrobials in the context
- 31 of treatment of MG?
- 32 • Azithromycin (all regimens)
- 33 • Moxifloxacin
- 34 • Other quinolones
- 35 • Tetracyclines (inc. doxycycline)
- 36 • Pristinamycin
- 37 • Other macrolides

- 1 10. Is a test of cure required, and if so, what is the optimal time to conduct a test-of-cure
- 2 following treatment?
- 3 11. How should the partners of patients with MG infection be managed?

Draft