

# *Mycoplasma genitalium* infections: current treatment options and resistance issues

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**Abstract:** *Mycoplasma genitalium* is one of the important causes of non-gonococcal urethritis. Rising incidence and emerging antimicrobial resistance are a major concern these days. The poor clinical outcomes with doxycycline therapy led to the use of azithromycin as the primary drug of choice. Single-dose azithromycin regimen over a period of time was changed to extended regimen following studies showing better clinical cures and less risk of resistance development. However, emerging macrolide resistance, either due to transmission of resistance or drug pressure has further worsened the management of this infection. The issues of drug resistance and treatment failures also exist in cases of *M. genitalium* infection. At present, the emergence of multidrug-resistant (MDR) *M. genitalium* strains is an alarming sign for its treatment and the associated public health impact due to its complications. However, newer drugs like pristinamycin, solithromycin, sitafloxacin, and others have shown a hope for the clinical cure, but need further clinical trials to optimize the therapeutic dosing schedules and formulate appropriate treatment regimens. Rampant and inappropriate use of these newer drugs will further sabotage future attempts to manage MDR strains. There is currently a need to formulate diagnostic algorithms and etiology-based treatment regimens rather than the syndromic approach, preferably using combination therapy instead of a monotherapy. Awareness about the current guidelines and recommended treatment regimens among clinicians and local practitioners is of utmost importance. Antimicrobial resistance testing and global surveillance are required to assess the efficacy of current treatment regimens and for guiding future research for the early detection and management of MDR *M. genitalium* infections.

**Keywords:** *Mycoplasma genitalium*, non-gonococcal urethritis, antimicrobial resistance, azithromycin, moxifloxacin, doxycycline

## Introduction

Though more than 3 decades have passed since the isolation of *Mycoplasma genitalium*, its management still remains an enigma for clinicians worldwide.<sup>1</sup> The organism's fastidious nature and slow growth have been a major hurdle in the diagnosis and in vitro antibiotic susceptibility studies.<sup>2</sup> Fortunately, nucleic acid amplification techniques (NAAT) emerged as a breakthrough for the diagnosis and prevalence studies.<sup>3,4</sup> Following the development of diagnostic polymerase chain reaction (PCR) techniques, *M. genitalium* has got its recognition as an established cause of sexually transmitted infections (STIs).<sup>5,6</sup> In recent years, there has been mounting evidence demonstrating the association of STI syndromes with *M. genitalium* infection.<sup>7,8</sup> According to the UK National guidelines for management of non-gonococcal urethritis (NGU), the prevalence of *Chlamydia*

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*trachomatis* and *M. genitalium* infection among patients with NGU ranges from 11% to 50% and 6% to 50%, respectively.<sup>9</sup> Further, reiterating the association of *M. genitalium* in STIs, is its inclusion under the heading “emerging issues” in the 2015 Centers for Disease Control and Prevention guidelines for treatment of STIs.<sup>10</sup> Several reasons responsible for this alarming problem include lack of international consensus on the treatment strategy, co-infection with human immunodeficiency virus (HIV), non-judicious use of macrolides for community-acquired pneumonia and poor adherence to treatment regimens among patients and their partners.<sup>11,12</sup>

The lack of peptidoglycan in *M. genitalium* precludes the use of antibiotics acting on the cell wall.<sup>1</sup> Other classes of antibiotics that have proven useful are tetracyclines, macrolides and quinolones. The dosage and regimens used for these drugs have differed in various parts of the world giving rise to increasing resistance to these antibiotics, especially to macrolides and quinolones.<sup>13,14</sup> Though resistance in other STI pathogens like gonococcus has increased insidiously, resistance in *M. genitalium* has emerged at a relatively greater speed belying its small size.<sup>15</sup> This could be because of the likely paucity of DNA repair systems that might foster emergence of resistance mutations. Increasing resistance in *M. genitalium* is a worrisome matter. Further aggravating the problem is the paucity of rapid, reliable and cost-effective assays for detecting resistance against more than one class of antibiotics, simultaneously.<sup>10,12,15</sup> The 2016 European guidelines for the management of NGU state that testing males with urethritis for *M. genitalium* along with simultaneous detection of macrolide resistance can improve the cure rate. At present, there is an ongoing search for newer antibiotics to treat NGU as a syndrome and cover all the implicated organisms through a single antimicrobial agent. Till now, pristinamycin is the only drug that has been shown to be effective against *M. genitalium* that is resistant to both macrolides and quinolones.<sup>16</sup> With the rising prevalence of *M. genitalium* among urethritis patients in certain European regions and higher rates of the asymptomatic carrier state in certain HIV-positive patients (especially in men who have sex with men, MSM), there is an imminent need for newer antibiotics and diagnostic assays for rapid diagnosis and management of *M. genitalium* infections.<sup>17,18</sup>

## Review of the microbiology of *M. genitalium* infections and resistance issues

The first isolation of *M. genitalium* dates back to 1980 by Tully et al from 2 male patients suffering from NGU.<sup>1</sup>

Taxonomically, it belongs to the family *Mycoplasmataceae* and order *Mycoplasmatales*, with the class *Mollicutes* (*mollis*: soft, *cutis*: skin) containing the 2 genera *Mycoplasma* and *Ureaplasma*.<sup>19</sup> They are probably the Gram-positive bacteria, likely from the clostridia group.<sup>20,21</sup> Regarded as the smallest free-living organisms, they were first observed under the transmission electron microscope.<sup>1,6,22</sup> With a genome size of only 580 kb, *M. genitalium* became the second organism to be completely sequenced following *Haemophilus influenzae*.<sup>23</sup> *M. genitalium* utilizes glucose as a substrate for survival by phosphorylating it with the help of enzyme glyceraldehyde-3-phosphate dehydrogenase to generate adenosine triphosphate.<sup>21</sup> Multiple virulence factors are present in the organism that help in the pathogenesis of genital infections. Adhesion is mediated by the proteinaceous terminal tip organelle consisting of MgPa protein and P32 (MG318) protein that are bound to the cell membrane.<sup>24,25</sup> The enzymatic activity of glyceraldehyde-3-phosphate dehydrogenase helps in adhesion to the vaginal and cervical mucosa, while another enzyme methionine sulfoxide reductase also increases the virulence.<sup>26,27</sup> The immune system evasion by the antigenic variation in the membrane proteins limits the host humoral system from generating an immune response against the organism.<sup>28,29</sup> The 2 components of MgPa protein, P110 and P140 undergo genetic variation thus generating novel proteins that are not recognized by the immune system.<sup>20,30</sup>

## Overview of the epidemiology, transmission and natural history of the infection

### Epidemiology

Since its discovery in 1980, little progress was initially made regarding the *M. genitalium* clinical associations and diagnosis.<sup>1,2</sup> Its fastidious nature makes it extremely difficult to isolate from clinical specimens. In cultures, it takes several weeks or even months to grow, which makes it further difficult to demonstrate its association with the clinical symptoms.<sup>31</sup> However, the implementation of the Vero cell co-culture technique helped in the isolation, clinical association and understanding of the mechanisms of resistance.<sup>32</sup> In early 1990, a PCR-based diagnostic assay was created to detect *M. genitalium* in clinical samples, these assays with better sensitivity empowered many studies demonstrating the association of *M. genitalium* with STI syndromes in both men and women.<sup>3,4,6</sup> *M. genitalium* infection rate varies with different population groups investigated for the study. In a population with low-risk sexual and high-risk sexual behavior practices, the infection rates are ~2% and 7%, respectively.<sup>33</sup> Among

the NGU group, the infection rate varies with geographical region and time period ranges from 6% to 50%.<sup>9</sup>

In men, *M. genitalium* infection is strongly associated with NGU and nonchlamydial NGU with estimated pooled odds ratio of 5.5 and 7.6, respectively.<sup>6</sup> The prevalence of *M. genitalium* infection in men with NGU varies from ~10% to 25%.<sup>6</sup> *M. genitalium* infection positivity has been reported to be ~41% and 50% in men with persistent or recurrent and chronic NGU (duration of symptoms >30 days), respectively.<sup>34,35</sup> In women, the association of *M. genitalium* infection with clinical signs and symptoms seems to be less strong than in men.<sup>5</sup> In females, its association with pelvic inflammatory disease, cervicitis, preterm labor, spontaneous abortion and tubal infertility have been demonstrated by several studies.<sup>5,36–40</sup>

### Transmission

*M. genitalium* is primarily transmitted by the sexual route as first studied by Keane et al who reported a concordance rate of 58% for *M. genitalium* infections among 39 couples, which was higher than the rate for *Chlamydia trachomatis*.<sup>41</sup> Similarly, Manhart et al also studied the transmission among young adults and showed that the risk was higher with vaginal intercourse.<sup>42</sup> Besides this route, *M. genitalium* has also been demonstrated in the anorectal samples through culture and NAAT, with a significant relationship between positive urethral samples and dysuria in MSM.<sup>43,44</sup> Edlund et al also established transmission through the penile–anal sexual route.<sup>45</sup> Vertical transmission is still an unestablished route of transmission; however, *M. genitalium* has been isolated from the respiratory tract of newborns.<sup>46</sup> It was hypothesized that it may influence the transmission of HIV

infections following its isolation from the blood of an HIV-positive patient.<sup>47</sup> Moreover, an in vitro study showed that adherence of *M. genitalium* to HIV-infected cells triggers the release of virus from these cells.<sup>48</sup> Consequently, incomplete eradication will increase the likelihood of HIV transmission. Though orogenital contact can lead to transmission of the organism, it is less likely due to the low carriage rate in the oropharynx.<sup>49</sup> The clinical features of *M. genitalium* infection are shown in Table 1.

### Natural history

Due to the slow growth rate and difficulty in isolating this organism, very few studies have documented the natural course of *M. genitalium* infection in literature. A study from Nairobi, Kenya involving a total of 258 female sex workers revealed that 17%, 9% and 21% of *M. genitalium* infections persisted after 3, 5 and 7 months, respectively.<sup>57</sup> In contrast to this, a similar study among female sex workers in Uganda revealed that 55% of the subjects cleared the infection within 3 months and that the infection clearance rates at the end of the sixth and twelfth month were 83% and 93%, respectively. Moreover, HIV-positive women cleared the infection more slowly in comparison with HIV-negative women, and the infection recurred in 39% patients after clearance.<sup>58</sup> A community-based study conducted in London revealed that multiple sexual partners and the presence of bacterial vaginosis are independent predisposing factors for *M. genitalium* infection.<sup>59</sup> The authors also reported that 26% of women who were positive for *M. genitalium* infection at the initiation of the study showed persistent infection after 12–21 months.<sup>59</sup> The incidence of persistent or recurrent NGU due to *M. genitalium* has been found to be 41% in men

**Table 1** Signs, symptoms and complications of *Mycoplasma genitalium* infection

Signs and symptoms: females	Signs and symptoms: males
Asymptomatic: 40% – 75%	Asymptomatic: 70%
Increased or altered vaginal discharge (<50%)	Urethritis (acute, persistent and recurrent)
Dysuria or urgency (30%)	Dysuria
Occasionally inter-menstrual bleeding or post-coital bleeding	Urethral discharge
Cervicitis	Proctitis
Lower abdominal pain (<20%)	Balanoposthitis
Complications: females	Complications: males
Pelvic inflammatory disease (endometritis, salpingitis)	Sexually acquired reactive arthritis
Tubal factor infertility	Epididymitis
Sexually acquired reactive arthritis	Rarely conjunctivitis in adults
Adverse pregnancy outcome	
Infertility (only indirect evidence)	

**Note:** Data from references 50 to 56.

after doxycycline treatment failure and ~50% of men were *M. genitalium* positive in chronic symptomatic NGU.<sup>34,35</sup>

A controversy exists regarding the association of *M. genitalium* infection with circumcision. In a study conducted in Kenya, 13.4% of uncircumcised men had *M. genitalium* infection when compared with 8.2% of circumcised men.<sup>60</sup> On the contrary, a study from England showed no relationship between the 2 conditions.<sup>61</sup> The association of *M. genitalium* with male infertility is also not exactly known. A meta-analysis of 307 infertile males, pointed out a possible role of *M. genitalium* in male infertility.<sup>62</sup> Hence, further studies are required to unequivocally prove its role in male infertility.

## Diagnosis

The indications for laboratory testing for *M. genitalium* as per the 2016 European guidelines have been shown in Table 2. The slow growth rate and fastidious nature of *M. genitalium* make its isolation very difficult. Jensen et al also developed a method for the isolation of this organism using Friis medium.<sup>32</sup> However, culture techniques remain cumbersome and hence, NAAT-based methods targeting the MgPa gene are the main tools for diagnosis.<sup>3,4</sup> However, the commercial diagnostic assays are limited and also not widely available in many countries where the syndromic management of NGU is followed. The specimens to be taken depend on the signs and symptoms, including urethral swab, urine, endocervical swab, endometrial biopsy and anal sample. Swabs made of calcium alginate, dacron or polyester with aluminum or plastic shafts are preferable for collecting clinical samples. SP4-based broth culture media is considered to be a good transport as well as a

**Table 2** Indications for laboratory testing for *Mycoplasma genitalium* as per the 2016 European guidelines

Signs and symptoms
Symptoms or signs of urethritis in men
Mucopurulent cervicitis
Cervical or vaginal discharge with a risk factor for STIs
Intermenstrual or post coital bleeding
Acute pelvic pain and/or PID
Acute epididymo-orchitis in a male aged <50 years
Risk factors
Any of the above symptoms in a regular sexual partner
Persons with high-risk sexual behavior (age <40 years and >3 new sexual contacts in last year)
Sexual contact with persons with an STI or PID, in particular <i>M. genitalium</i> infected persons
Before termination of pregnancy or other procedures that breach the cervical barrier
Regular testing of MSM, including anal sampling

**Note:** Data adapted from Jensen et al.<sup>70</sup>

**Abbreviations:** MSM, men who have sex with men; PID, pelvic inflammatory disease; STI, sexually transmitted disease.

culture medium for *M. genitalium* and was developed by Tully et al.<sup>1</sup> Another medium that has been used widely for culturing *M. genitalium* is pleuropneumonia-like organisms broth with added supplements.<sup>63</sup> Commercial kits for diagnosing *M. genitalium* infection are available but none of them have received US Food and Drug Administration (FDA) approval for diagnostic use. Le Roy et al evaluated 2 such commercial kits: TIB MOLBIOL LightMix kit (Roche Diagnostics, Risch-Rotkreuz, Switzerland) targeting the *mg219* gene and the Diagenode real-time PCR kit (Diagenode, Liège, Belgium) targeting the *gap* gene.<sup>64</sup> These kits have a sensitivity of 92.6% and 87%, respectively, with a specificity of 100%. Invader-Plus technology-based assay targeting the 16S rRNA gene of *M. genitalium* carried out on urine samples demonstrated a lower detection limit of 10 DNA copies per reaction.<sup>65</sup>

## Resistance issues

Often termed as the “naked bacteria”,<sup>66</sup> *M. genitalium* is not susceptible to antibiotics that inhibit cell wall formation. Besides the limited range of antibiotics present for managing this organism, the lack of easy and routine methods to determine antimicrobial susceptibility further adds to the problem. However, the inhibition of *M. genitalium* growth in Vero cell cultures provides an opportunity to determine antimicrobial susceptibility by comparing the proportion of DNA level of *M. genitalium* controls growing under identical culture conditions.<sup>67,68</sup> Tetracyclines, especially doxycycline are still used widely for treating NGU but gradually their cure rates have decreased and resistant isolates were identified.<sup>69</sup> Macrolides, especially azithromycin were the second group to be used extensively for managing *M. genitalium* infections, but again the regimens used were a matter of controversy with present guidelines discouraging the use of a single 1 g dose regimen.<sup>70</sup> Quinolones were initially active against macrolide-resistant organisms but reports of resistance to moxifloxacin are available in recent times.<sup>71</sup> Newer drugs like josamycin and pristinamycin are being used nowadays for the treatment of multidrug-resistant (MDR) organisms, but only in certain limited geographic regions.<sup>70</sup> The following descriptions will elaborate the resistance pattern against each antibiotic class separately.

## Tetracyclines

Doxycycline was the most extensively used drug among this group but showed poor response rates in the range of 30%–40%.<sup>72,73</sup> Ironically, in vitro data from one study showed that minimum inhibitory concentration (MIC)<sub>50</sub> and MIC<sub>90</sub> of doxycycline for *M. genitalium* were 0.25 and 1 mg/L, respectively, contradictory to the clinical efficiency.<sup>74</sup> To date, neither any specific mutations nor the exact explanation for this discrepancy has been reported.<sup>15</sup>

## Macrolides

The prominently used macrolide for *M. genitalium* infection is azithromycin. Traditionally, 2 regimens of azithromycin have been used. Single-dose regimen of 1 g and extended-dose regimen of 1.5 g were given over a period of 5 days. The latter regimen had shown efficacy in *Mycoplasma pneumoniae* infection, and hence it was predicted that it would be more effective against the slowly growing *M. genitalium* too; so, it was adopted in many European countries.<sup>73,75</sup> The cure rate with the single-dose regimen was initially 85% but this gradually declined as per the studies from various geographic regions.<sup>72,73</sup> A study by Manhart et al showed only a 40% cure rate in subjects compared with 30% cure rate in those receiving doxycycline.<sup>76</sup> Similarly, another study from Melbourne (Australia) by Twin et al showed a decrease in cure rate from 84% (2005–2007) to 69% (2007–2009).<sup>77</sup> In Greenland, where chlamydial infections are common and a single dose of azithromycin is used for its treatment, almost all *M. genitalium* infections are caused by macrolide-resistant strains.<sup>78</sup> Recent guidelines discourage use of the single 1 g dose regimen in light of the emerging macrolide resistance associated with this regimen.<sup>70,79</sup> A study by Anagrus et al showed that none of the 77 patients treated with the extended regimen developed macrolide resistance.<sup>80</sup> In another study, comparing both regimens in macrolide-susceptible strains showed new onset resistance in 6.5% of subjects receiving the extended regimen and 10% in those receiving the single-dose regimen.<sup>81</sup> The probable cause for the failure of the single-dose regimen may be related to the load of organisms in the affected individuals as shown in a study by Bissessor et al where an increase in the organism load by every log<sub>10</sub> was associated with chances of failure of this regimen.<sup>16</sup> Moreover, injudicious use of this regimen without confirming the eradication of *M. genitalium* might have given rise to spontaneous mutations in the surviving organisms. Ever since the first report of macrolide resistance in 2006, there has been a rise in the resistance rate.<sup>82</sup> As per a recent study among 946 subjects from different geographic regions of USA, the rate of macrolide-resistant *M. genitalium* infection was 50.8% in females and 42% in male subjects.<sup>83</sup> The mechanism of macrolide resistance involves an alteration in the ribosomal proteins that prevent the binding of the drug to the ribosomes. Mutations have been identified in V region of the 23S rRNA and the L4 and L22 ribosomal components.<sup>84,85</sup> The predominant mutations identified in the 23S rRNA gene are A2058G, A2059G and A2058T; with the latter being the

most common.<sup>86</sup> The injudicious use of azithromycin for respiratory tract infections and single copy number of the gene are likely responsible for rising macrolide resistance. Thus, newer macrolides like josamycin have been tried for the management of azithromycin-resistant *M. genitalium* infection. However, mutations associated with resistance in josamycin have also been reported recently.<sup>87</sup> It has been noticed that A2058G and A2059G mutations lead to resistance to the 15-membered macrolides such as azithromycin. Also, it has been found that the same A2059G mutation leads to high-level resistance to the 16-membered macrolides too, such as josamycin. In addition to this, mutation at position A2062 of the 23S rRNA gene can lead to high-level resistance to josamycin (16-membered macrolide) but surprisingly, not to azithromycin (15-membered macrolide), suggesting a difference in the binding site. However, to date, it is unknown whether A2058G/A2059G and A2062G mutation can co-occur in the 23S rRNA gene.<sup>87</sup>

## Fluoroquinolones

Moxifloxacin, a fourth-generation fluoroquinolone, has been the most frequently used second-line drug. Its use for management of these infections was reported for the first time in 2006 and many initial studies had shown a cure rate approaching 100%.<sup>88,89</sup> But, recent reports document treatment failures with moxifloxacin, especially in the Asia-Pacific region, with many subjects having an infection with strains resistant to both macrolides and fluoroquinolones.<sup>16,71</sup> Another study from Japan showed an increasing rate of fluoroquinolone resistance among *M. genitalium* isolates, with a rise from 20% in 2011 to 47% in 2013.<sup>13</sup>

The first report of a mutation associated with moxifloxacin resistance in *M. genitalium* was from Sydney, Australia.<sup>71</sup> Mutations in the DNA gyrase genes (*gyrA* and *gyrB*) and topoisomerase IV genes (*parC* and *parE*) are associated with resistance. A study from Japan, identified mutations in the quinolone resistance determining regions of the *parC* gene as the cause of resistance in moxifloxacin and other fourth-generation quinolones.<sup>90</sup> The mutations in the positions Ser83 and Asp87 (MG numbering) are found in the resistant isolates. The moxifloxacin resistance rate varies in different parts of the world; a rising trend (47%) has been noted in Japan while a lower incidence of 5% in London (UK) and 15% in an Australian STI clinic has been reported.<sup>91,92</sup> Despite the reported resistance mutation, no correlation has been established between the rising MIC values and treatment failure rates.

### Detection of antimicrobial resistance (AMR)

All strains of *M. genitalium* isolated from clinical samples before 2003 were susceptible to macrolides but since then the number of resistant strains has increased. With this in mind, all samples with a positive result in NAAT for *M. genitalium* should ideally be tested for macrolide resistance mutations. With the increasing macrolide resistance, there is a need for an assay to diagnose *Mycoplasma* and detect macrolide resistance simultaneously. Recently, a multiplex assay named MG 23S assay was developed that employs novel PlexZyme™ and PlexPrime™ technology to diagnose *M. genitalium* infection and detect 5 mutations involved in macrolide resistance.<sup>93</sup> A total of 400 samples were evaluated with this assay and the results were compared with the reference quantitative PCR method with high-resolution melt analysis. The sensitivity for *M. genitalium* diagnosis and mutation detection was shown to be 99.1% and 97.4%, respectively, and the specificity for the same was 98.5% and 100%, respectively.<sup>93</sup> Use of such assays, should be helpful in choosing the appropriate antibiotics for managing the infection. Further data and research will decide the possible future use of this kit for diagnosis. Mutations mediating resistance to moxifloxacin can also be detected by molecular methods that are based on *parC* gene sequencing.<sup>74,91,94</sup> However, there does not exist a fine correlation between various mutations in *parC* and in vitro moxifloxacin resistance.<sup>91</sup> To date, no commercial assay has been approved by FDA due to the lack of validation of these developed platforms. Recently, an automated Aptima platform targeting the 16S rRNA is under comprehensive validation and may generate superior results.<sup>15</sup>

### Management of *M. genitalium* infection

Patients with *M. genitalium* infection are advised to maintain abstinence from unprotected intercourse until both sexual partners have completed the treatment and are symptom-free. Both sexual partners should be screened for other STIs and informed about the risk of transmission and imminent complications. In cases where a partner does not get tested, the same treatment is to be offered as given to the index

patient. A test of cure should also be performed routinely for all patients in view of the increasing prevalence of macrolide resistance, which may exist prior to initiation of therapy or can evolve during therapy with a macrolide.<sup>70</sup> Furthermore, *M. genitalium* infection during pregnancy can jeopardize the health of the fetus as well as the mother, especially in terms of susceptibility to preterm labor and spontaneous abortions.<sup>5</sup> The problem is further aggravated by the absence of safe options for treatment of infection caused by macrolide-resistant strains during pregnancy, hence treatment of such infections is often withheld till completion of pregnancy. Pristinamycin, due to its safety profile, has proven to be a ray of hope for treatment of such resistant infections during pregnancy. The neonates of infected patients should be observed for development of conjunctivitis and respiratory tract infections.<sup>70</sup>

### Current treatment options

In view of the increasing resistance among *M. genitalium* for macrolides and quinolones, the treatment regimen should be short and convenient to the patient in order to ensure adherence. The most recent European guidelines – 2016 have divided the treatment depending on whether the infection is complicated or not and presence/absence of macrolide resistance among the isolates.<sup>70</sup> Similarly, another European guideline for the management of NGU in 2016 has also given a stepwise approach for treatment.<sup>9,95</sup> Macrolides are still recommended as the first-line antibiotics for *M. genitalium* infections. Newer antibiotics like josamycin and pristinamycin have also been included in the guidelines. The recommended therapies as per the European guidelines for management of *M. genitalium* infections are shown in Table 3.<sup>70</sup>

### Emerging treatment options

#### Pristinamycin

It is a bactericidal streptogramin used against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, especially in France. It is effective against macrolide-susceptible

**Table 3** European guidelines for management of *Mycoplasma genitalium* infection

Type of infection	Macrolide resistance	First-line antibiotics	Second-line antibiotics	Third-line antibiotics
Uncomplicated infection	No	Azithromycin or josamycin	Moxifloxacin	Doxycycline or pristinamycin
	Yes	Moxifloxacin		
Complicated infection (pelvic inflammatory disease, epididymitis)	Moxifloxacin 400 mg once a day for 14 days			

Note: Data from Jensen et al.<sup>70</sup>

*M. genitalium* and is also used as a third-line agent against MDR strains.<sup>16,96</sup> In a Scandinavian trial, patients responded well to this drug and infections were successfully eradicated in 6 patients in Australia.<sup>16</sup> The maximal recommended dose is 1 g 4 times a day for 10 days. Due to the high price, lack of clinical registration of drug and patient compliance for the drug issues, this drug has not been established as a second-line drug.<sup>15</sup>

#### Josamycin

Besides azithromycin, this is the other macrolide agent that is used as a first-line drug against *M. genitalium* infection, especially in Russia. A study in 2015 showed that the drug (500 mg 3 times a day for 10 days) eradicated infection in 93.5% male patients with urethritis who had lower *M. genitalium* load ( $\leq 4$  g eq/mL [ $\log_{10}$ ]) prior to treatment, while patients in whom load was high ( $\geq 6$  g eq/mL [ $\log_{10}$ ]), the eradication rate achieved was 50%.<sup>87</sup> Resistance has been reported against this agent due to mutation at A2059G and A2062G of the 23S rRNA gene.<sup>87</sup>

#### Solithromycin (CEM – 101)

The drug is an extended-spectrum fluoroketolide superior to doxycycline, quinolones and azithromycin, possessing activity against both macrolide-susceptible and -resistant *M. genitalium*, though cross-resistance exists and mutation at the A2058 position is responsible for higher MIC.<sup>97</sup> A clinical cure of 65%–85% has been theoretically estimated in the case of azithromycin resistance infections; however, large-scale clinical trials are needed to further assess the clinical efficacy.

#### Lefamulin (BC-3781)

This pleuromutilin antibiotic inhibits protein synthesis by interfering with 23s rRNA.<sup>98</sup> It has been previously used for a long time in the veterinary industry and is recently being studied for human use. In a study by Paukner et al it was found to be efficacious against MDR bacterial pathogens causing STIs, including *M. genitalium*.<sup>98</sup> Though the drug is advantageous as it is available in both oral and intravenous formulations, more clinical trials are needed in order to evaluate its potential. This drug has successfully cleared the Phase II randomized controlled trial for its use in skin and soft tissue infections.<sup>99</sup> However, its clinical efficacy in *M. genitalium* infections is yet to be evaluated.

#### Sitafloxacin

This fourth-generation fluoroquinolone may also become a treatment option in the near future. The drug has already been

registered for use in Japan for treatment of *M. genitalium* infection with an overall cure rate of around 95% in recent studies.<sup>100,101</sup>

#### Zoliflodacin

Zoliflodacin is a newer spiropyrimidinetrione class of drug and is DNA gyrase/topoisomerase inhibitor. It has been found to be efficacious against *Neisseria gonorrhoeae* isolates including those resistant to fluoroquinolones. Also, it is equally effective against macrolide- and quinolone-susceptible strains of *M. genitalium* but both in vivo and in vitro studies regarding its efficacy in MDR strains are lacking.<sup>102</sup>

#### Spectinomycin

This aminocyclitol aminoglycoside is used as an alternative treatment for gonococcal infections. This can be a promising option for MDR *M. genitalium* as Falk and Jensen successfully treated a case of macrolide-resistant *M. genitalium* urethritis with this drug.<sup>103</sup> However, further studies are required to determine the appropriate treatment regimen for this drug.

## Future perspectives

The alarming rise in antibiotic resistance among *M. genitalium* isolates highlights the indiscriminate use of macrolides for respiratory tract infections, lack of consensus on the management of NGU and lack of resources for facile evaluation of AMR in this organism. Henceforth, a national consensus guideline, including the antibiotic policy, diagnostic steps and partner tracing should be framed. A research priority should be the development of an easy, economic and quick diagnostic test that is available at point of care to diagnose *M. genitalium* infections and resistance simultaneously so that treatment can be optimally guided. Similar to *N. gonorrhoeae*, dual therapy for *M. genitalium* infection too, should likely be introduced in the near future.<sup>10,104</sup> As the exact role of *M. genitalium* in conditions such as adverse pregnancy outcome and infertility are not perfectly known, further elaborative studies are required to establish the association.

## Conclusion

*M. genitalium* has emerged as a superbug and the rising resistance in this bacterium with only a few treatment options in hand is an imminent problem. Future research should look toward developing newer antimicrobials and proper management algorithms. Monotherapy should no longer be used. Combination therapy along with AMR testing is the need of the hour. Etiology-based treatment will be a definitive solution to this emerging AMR due to the misuse of antibiotics as

a part of syndromic management. National and international surveillance networks need to monitor and place emphasis on the existing prevalence, growing trend of resistance, and testing for AMR in treatment failure cases, which should be increased. Solithromycin and sitafloxacin seem to be promising treatment options and drugs such as lefamulin and zoliflodacin are in the pipeline and should be further evaluated for their efficacy.

## Disclosure

The authors report no conflicts of interest in this work.

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