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Current state of the research on *Mycoplasma genitalium* infection

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Mycoplasma genitalium is currently recognized as a non-opportunistic pathogen, and therefore detection of this pathogen is an absolute indication for causal treatment. Treatment of patients with *M. genitalium* infection prevents further transmission of the causative agent and development of complications, including pelvic inflammatory diseases and tubal infertility. Rapid development of resistance of this pathogen to various pharmacological groups of antimicrobials around the world in one of the key current challenges in treatment of *M. genitalium* infection.

Keywords: Mycoplasma genitalium, review, clinical presentation, treatment, resistance.

Characteristics of *Mycoplasma genitalium*

Mycoplasmas are the smallest prokaryotes capable of independent reproduction. They belong to the class *Mollicutes («soft skin»)* and evolved regressively by reducing the genome of gram-positive progenitor bacteria [1]. Genetic information is provided by the genome. The genome of *Mycoplasma genitalium* is the smallest known one among self-replicating structures [2].

Over a number of years, Mollicutes were referred to as viruses, since they can pass through filters with a pore diameter of 0.45 and even 0.22 μm. Since the 1930s, when the concept of viruses was more clearly formulated, mycoplasmas are referred to as bacteria. In the 1950s, some mycoplasmas species were referred to as L-form bacteria, i.e. bacteria without a cell wall, and only in the 1960s, mycoplasma occupied its current taxonomic position. The ability to pass through bacteriological filters and the absence of the cell wall are the key features determining that new bacterial species belong to mycoplasmas [2].

M. genitalium was first cultured based on urethral exudates of 2 out of 13 male patients with non-gonococcal urethritis (NGU) in 1981 using a broth medium (SP-4) developed for other mycoplasmas [2]. Growth was observed after 50 days of incubation as evidenced by change in medium color due to glucose fermentation. Detection of *M. genitalium* in the subgroup of males with NGU was an interesting fact, but it was insufficient to determine the relationship between *M. genitalium* and development of urethritis. Unfortunately, the relationship between the microorganism and human disease was not determined due to the exotic nature of *M. genitalium*. It took 10 years after isolation of *M. genitalium* from male urethra to discover sensitive and specific detection methods, which showed that *M. genitalium* infection causes various urogenital diseases [3].

M. genitalium is mostly flask-shaped with a pronounced narrowed tail [4]. It is on the average 0.6 to 0.7 μm long; its thick portion is 0.3 to 0.4 μm in diameter and its thin portion 0.06 to 0.07 μm in diameter. Despite the small size of the genome, *M. genitalium* still has a sufficient genomic composition for active movement, involving MG200 and MG386 genes [5]. Special terminal structures are also important. They are used by microorganisms for sliding movements, where the thin end moves first.

Despite the fact that *M. pneumoniae* and *M. genitalium* are structurally and, in some cases. antigenically similar, their genomes certainly differ. *M. genitalium* has the smallest genomic size of all mycoplasmas (580 kb); the genone of *M. pneumonia* is larger (816 kb) [6]. For comparison, the genomes of *Chlamydia trachomatis* and *Escherichia coli* are 1,450 kb and 4,700 kb, respectively. The content of guanine+cytosine (G+C) differs in *M. pneumoniae* and *M. genitalium,* 39 and 32%, respectively.

There was a time when the model of mycoplasma replication was the subject of discussions. Currently, classical binary fission is considered as reproduction method. *M. genitalium* is no exception. Although *M. genitalium* is mostly flask-shaped, the existence of other morphological forms can be attributed to the fact that cytoplasmic fission does not always occur synchronously with genome division. Perhaps, many smaller and aberrant cells do not obtain the required genetic material and for this reason they are not capable of reproduction [1].

M. genitalium is capable of intranuclear localization preserving the viability of host cells, which is a distinctive feature as opposed to other bacterial pathogens. It is known that the nuclear translocation of pathogens (e.g., *Mycobacterium tuberculosis, E. coli*) is accompanied by production of specific toxins leading to DNA damage and host cell death [7].

A unique ADP, ribosylating and vacuolizing toxin of *M. pneumonia (*MPN 372) was described, which causes pathological effects and more severe course of respiratory disease [8]. It is not known, whether *M. genitalium*

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produces a similar toxin. However, calcium-dependent membrane-associated nuclease of *M. genitalium* (MG-186) was identified and it was shown that it allows *M. genitalium* to cleave host cell the nucleic acids and to use them as a source of nucleotide precursors for its growth, as well as for the development of pathogenetic processes [1]. The absence of cell walls and similar structure of cell membranes to those of host organism cells enables penetration of mycoplasmas into the host cell membrane and protects them from the effects of humoral and cellular immunity factors. Adhesins, protease, and phospholipase are the leading pathogenic factors [9].

Mollicutes are membrane parasites and compete with the host cell for the substrate, deplete its energy and material reserves, disturb the amino acid metabolism, synthesis of proteins and nucleic acids, introduce new genetic information, and distort the structure of the active surface, which leads to disturbance of absorption, metabolism, excretion, and biological signal exchange with other cells and body systems [1].

Immunological reactions can contribute to pathogenicity of *M. genitalium*. It is known that damage caused by *M. pneumonia* is mostly immunologically mediated and it is a secondary cellular response of the immune system to the primary infection. Similar situation can occur in the case of *M. genitalium* infection. It is also known that an acute inflammatory response caused by polymorphonuclear leukocytes (PNL) results from a primary reaction to mycoplasma. This was shown in the experiment on *M. genitalium* invasion in the genital tract of male and female anthropoid primates [10]. Moreover, it was found that cultured human vaginal and cervical epithelial cells are sensitive to *M. genitalium in vitro*. This explains the conjecture, how the injury activates an acute inflammatory response. The principle of cytokine response is based on enhancement and stimulation of monocytes and macrophages in the vaginal and cervical mucosa. Phagocytosis by macrophages is an effective way of *M. genitalium* elimination, but intracellular localization can contribute to survival of *M. genitalium,* protecting it from cellular immune response and thus facilitating the development and maintenance of infection [11].

Some mycoplasma cell components can act as superantigens and subsequently lead to the development of autoimmune pathology.

There is an evidence that *M. genitalium* is involved in the potentiation of HIV infection, development of arthritis, atypical pneumonia, chronic fatigue syndrome, and autoimmune diseases.

A person who has an acute or chronic form of the disease with a clonical or asymptomatic course is the source of infection. Dissemination in the body occurs in a canalicular, transplacental, lymphogenous, hematogenous, as well as spermatozoa-mediated way. Onset of the disease is typically associated with the beginning of sexual activity or sexual partner change. The duration of the incubation period varies from 3 to 60 days. Some authors believe that individuals with acute inflammatory diseases has shorted incubation period compared to those with subacute infection.

Clinical conditions caused by *M. genitalium* infection

Clinical picture of mycoplasmal infection has no specific symptoms. Since *M. genitalium* was originally isolated from males with NGU, it is not surprising that the authors of subsequent studies focused on this condition. Pathogenetic role of *M. genitalium* in the development of NGU in males was evidenced by detection of this microorganism by polymerase chain reaction (PCR) in 23—25% of patients and only in 6% of healthy males. Positive dynamics of clinical symptoms resulting from treatment with doxycycline in patients with urethritis in the presence of *M. genitalium* is another evidence. Furthermore, the research shows a correlation between elimination of *M. genitalium* from the urethra and resolution of clinical symptoms of urethritis, and conversely, disease recurrence may be associated with the use of drugs that are not sufficiently active against this pathogen [12].

Urethritis caused by *M. genitalium* is characterized by acute, subacute, or torpid course. The detection rate of *M. genitalium* is higher in patients with a pronounced clinical presentation, which does not differ from the clinical presentation of acute gonococcal urethritis (hyperemia and edema of the urethral opening, copious discharge, turbid first portion of urine in the case of anterior urethritis and both portions in the case of total urethritis) and amounts to 70% [13]. Thus, the detection rate of *M. genitalium* was 13 to 35.3% in patients who complained of the above symptoms and had 5 or more polymorphonuclear leukocytes in the field of view in biological material obtained from the urethra [14]. In patients with a torpid form of urethritis characterized by less pronounced inflammation signs with a trace amount of mucous or mucopurulent discharge from the urethra, the detection rate of *M. genitalium* was 8 to 10% [15]. Clinical presentation of chronic urethritis is mild. Subjective sensations, as a rule, include only mild dysuria. There are typically no inflammatory phenomena at the urethral opening. Scanty discharge in the form of a mucous drop can be only observed when squeezing, sometimes only in the morning; there are mucous filaments in the urine [16]. Chronic urethritis can be accompanied by exacerbations, as well as the development of complications [17].

The etiology of urethritis in men who prefer sex with men is a separate issue. It is *M. genitalium* rather than *C. trachomatis* and/or *U. urealyticum* that is most often detected in homosexual males with NGU, practicing oral sex [16].

The authors described the pronounced symptoms of urethritis in males compared to the clinical manifestations of the disease caused by *C. trachomatis* [13]. Clinical forms of urethritis are more common in patients infected with *M. genitalium* compared to those with urogenital chlamydial infection: 73 and 40%, respectively [18].

Inflammation of the balanus (balanitis) and foreskin (postitis) often occur concomitantly (balanoposthitis). One study reliably showed the relationship between *M. genitalium* and balanoposthitis in 114 males with acute symptomatic NGU. This relationship was also observed with the control for *C. trachomatis,* which was not involved in the pathological process.

Despite the fact that *M. genitalium* leads to chronic NGU, there are scarce data that it is also associated with chronic prostatitis. In one study based on PCR of prostate biopsy specimens taken under ultrasound control from 50 patients with chronic non-bacterial prostatitis, this relationship was not confirmed [19]. In another study, *M. genitalium* was detected by PCR of prostate biopsy specimens in 5 (4%) of 135 males [20]. In another study, *M. genitalium* was detected in semen of 2 out of 18 males with chronic non-bacterial inflammatory prostatitis compared to 0 of 20 control group patients, but these data are still insufficient to suggest any significant relationship [21]. However, it is possible that detection of *M. genitalium* is hampered by previous administration of antibiotics and probably (theoretically) early infection can initiate immunological processes leading to chronic prostatitis. *M. genitalium* can also cause acute epididymitis in some patients [22].

In females, *M. genitalium* causes urethritis, cervicitis, and leads to the development of complications, such as pelvic inflammatory diseases (PIDs) and probably tubal infertility and sexually-associated reactive arthritis. There are many scientific papers that show the relationship between *M. genitalium* and urethritis in females who applied to sexual health clinics [18].

The first evidence of the relationship between *M. genitalium* and cervicitis in females was obtained in the Japanese research published in 1997 [23]. *M. genitalium* was found in 5 (9%) of 57 females. Later on, the results of other studies have largely confirmed that *M. genitalium* plays a significant role in the development of cervicitis [18, 24]. Clinical manifestations of cervicitis develop about 3—4 weeks after infection. There is dysuria, some female complain of itching and burning in the perineum, pathological vaginal discharge, and abdominal pain. Cervicitis is accompanied by mild mucopurulent discharge. The appearance of infected cervix may vary from clinically normal to severely eroded with a thickened edematous mucosa and copious mucopurulent discharge.

Like most diseases of the urogenital tract, PIDs are polyetiologic and more difficult to diagnose than cervicitis. Undoubtedly, *M. genitalium* colonizing the cervical canal can also invade the upper genital tract and cause PID. Thus, up to 60% of females with *M. genitalium* in cervical smears and clinical signs of upper genital tract infection had positive results of endometrial biopsy [25].

An early study detected *M. genitalium* in the endometrial biopsy specimen of a female with clinically significant PID, but it is impossible to find out whether there was a true relationship between the detected microorganism and inflammatory process [26]. Another study showed that *M. genitalium* was associated with a diagnosed histologically acute endometritis, which was found in 9 (16%) out of 58 females [27].

There are several studies, where fallopian tubes were examined using laparoscopy. In one of them, *M. genitalium* was detected in the cervical canal/endometrium in 9 (7%) out of 123 females with acute salpingitis but only in one fallopian tube [28]. In another study (D. Taylor-Robinson, J. Jensen, H. Svenstrup, and C. Stacey, unpublished data), *M. genitalium* was found in only one fallopian tube in 22 females with salpingitis.

The main facts proving that *M. genitalium* causes PIDs are as follows:

1) the ability of microorganisms to adhere to fallopian tube epithelium in the organ culture and injure cells and cilia [29];

2) experimental development of endometritis and salpingitis in some anthropoid apes and formation of pyosalpinx in mice [30];

3) association of the tubal infertility factor with previous *M. genitalium* infection [31];

4) the presence of antibody response to *M. genitalium* in a third of females with acute PIDs (32).

It was proved that *M. genitalium* is attached to the head, middle part, and tail of the human spermatozoa through its tail part *in vitro* and affects their movement in a significant number of cases [33]. Probably, spermatozoa, which still move and carry microorganisms, can deliver them to the upper genito-urinary tract. Given the fact that *M. genitalium* causes PIDs, it should be taken into account that it can result in fallopian tube injury and occlusion and subsequent infertility.

There is insufficient data on the relationship between *M. genitalium* and premature labour or spontaneous abortion, while the prevalence of the microorganism in pregnant females (according to numerous international studies) is quite low, and therefore the effect of *M. genitalium* infection on the course and outcome of pregnancy is still an open question. At the same time, serological studies showed the relationship between *M. genitalium* infection and increased risk of tubal infertility [34].

Recently, it has been suggested that *M. genitalium*, like *C. trachomatis*, can cause the development of sexually acquired reactive arthritis (SARA). In one of the scientific papers, the authors detected *M. genitalium* in 9 (35%) synovial fluid specimens from the temporomandibular joint cavity of 26 patients complaining of pain in this area, using PCR [35].

Taking into account the fact that reactive arthritis is an integral part of Reiter's syndrome, the case described by the authors in 2004 [36] deserve attention. The researchers found *M. genitalium* in the urine and conjunctival discharge of a patient with non-chlamydial and non-gonococcal conjunctivitis and urethritis. Medical history shows that this patient had recurrent dysuria and symptoms of conjunctivitis during 5 months, which resolved

after antibiotic therapy (doxycycline 100 mg once a day for 10 days) and local therapy with antiallergic eye drops. It should be noted that the nucleotide sequences of *M. genitalium* found in urine and conjunctival discharge were completely identical.

Diagnosis of *M. genitalium* infection

Examination for *M. genitalium* in indicated in the following cases: the symptoms of urethritis in males; mucopurulent cervicitis; cervical/vaginal discharge with STI risk factors; postcoital bleeding or menometrorrhagia; acute pelvic pain and/or PIDs; acute epididymoorchitis in males younger than 50 years; men who prefer sex with men; sexual contact with STI or PID patients; before the end of pregnancy, before the procedures breaking the cervical barrier; in persons at risk (less than 40 years of age, more than three new sexual contacts during the year, more than five partners throughout life, and never examined individuals) [37].

M. genitalium is the smallest bacterium known to date with a genome of 580 kbp. For the first time, *M. genitalium* was isolated in a culture in 1981, and signs of growth in the form of change in medium color due to glucose fermentation occurred only 50 days after inoculation. *M. genitalium* is extremely demanding for culturing conditions, so the culture method is very labor and time consuming. Despite the fact that the technique of *M. genitalium* culturing significantly improved in recent years, including the use of cell cultures, isolation and amplification of this microorganism still takes several weeks to several months [38].

M. genitalium cannot be visualizes using light microscopy due its small size.

M. genitalium and the most genetically similar *M. pneumoniae* have a number of common structural features. The significant antigenic similarity between these two mycoplasmas is a serious obstacle to serological diagnosis. As early as in 1982, at the earliest stages of the study of *M. genitalium*, significant cross reactivity between *M. genitalium* and *M. pneumoniae* in the reactions of complement fixation, metabolism inhibition, and indirect haemagglutination was demonstrated [39].

Thus, adequate identification of *M. genitalium* was virtually impossible due to the inapplicability of conventional bacteriological diagnostic methods, until molecular-biological tests were developed [40]. The data from PCR studies for detection of *M. genitalium* in males with NGU were first published in 1993 [14]. Further application of PCR provided an evidence that *M. genitalium* is a sexually transmitted pathogen capable of inducing a number of reproductive tract diseases in both males and females.

Among a wide variety of hybridization methods for DNA analysis, PCR is most widely used both for scientific research and diagnosis in practical health care. The general principle of PCR is based on amplification of the target specific DNA fragment using DNA polymerase enzyme.

The first study where real-time PCR method was used to analyze DNA of *M. genitalium* was published in 2002 [11]. This technique enables direct real-time recording of accumulation of a specific amplification product during the reaction, which significantly reduces the analysis time and the risk of contamination. Additionally, real-time PCR enables target quantification in the sample.

Since 2015, Nucleic Acid Sequence Based Amplification (NASBA) was included in current Russian clinical guidelines for management of patients with urogenital infections. NASBA is the method of ribosomal RNA amplification. RNA is the direct marker of the presence of an infectious agent in a biomaterial under study. There are the following differences between NASBA and PCR:

1. The number of targets for NASBA is hundreds and thousands of times higher than for PCR, and therefore NASBA has higher analytical sensitivity;

2. RNA, unlike DNA, is a less stable molecule, and therefore positive result of NASBA is a more accurate marker of infection and enable early evaluation of the effectiveness of antibiotic therapy.

Biological material from the cervical canal and urethra is typically used to detect *M. genitalium*. Additionally, non-invasive samples (urine and self-collected vaginal samples) are as sensitive as those using cervical and urethral specimens. Noninvasive sampling is preferred by patients themselves, which greatly facilitates the screening [41].

Treatment of *M. genitalium* infection

M. genitalium is recognized as a non-opportunistic pathogen, and therefore detection of this microorganism is an absolute indication to etiotropic therapy. Treatment of patients with *M. genitalium* infection prevents further transmission of the pathogen and development of complications, including PIDs and tubal infertility [34].

The diseases associated with *M. genitalium* are typically treated using tetracyclines, macrolides and fluoroquinolones.

Tetracyclines are broad-spectrum antibiotics that have a bacteriostatic effect on sensitive microorganisms. Tetracyclines are active against gram-positive and gram-negative bacteria, as well as spirochetes, rickettsia, chlamydia, and mycoplasmas.

Macrolides are broad-spectrum antibiotics produced by some types of *Streptomyces* and their molecules include a macrocyclic lactone ring. Macrolides have a bacteriostatic effect resulting from binding to the 50S subunit of the ribosome, which disturbs protein synthesis. Azithromycin and josamycin are the most widely used drugs of this group.

Fluoroquinolones are the fluorinated derivatives of the nalidixic acid and other quinolones, which are mostly active against gram-negative bacteria. Fluoroquinolones have a bactericidal effect and inhibit DNA gyrase and topoisomerase IV, the enzymes involved in DNA replication.

Table 1. **Recommendations on the treatment of *M. genitalium* infection (IUSTI/WHO (2016)**

Therapy line	Drug	Treatment regimen
First (when there is no resistance to macrolides)	Azithromycin	500 mg on the first day, then 250 mg daily for 4 days
	Josamycin	500 mg 3 times a day for 10 days
Second (when there is resistance to macrolides)	Moxifloxacin	400 mg once a day for 7—10 days
Third (when the first and second line treatment is ineffective)	Pristinamycin	1.0 g 4 times a day for 10 days
	Doxycycline (the effectiveness is about 30%)	100 mg 2 times a day during 14 days

Table 2. **Clinical guidelines of the Russian Society of Dermatologists, Venereologists, and Cosmetologists (Dermatovenereology 2015: Skin diseases, sexually transmitted infections)**

Clinical situation	Drug and treatment regimen	
Uncomplicated forms of urogenital diseases caused by *M. genitalium*	First line treatment	
	Doxycycline monohydrate	100 mg per os 2 times a day for 10 days
	Josamycin	500 mg per os 3 times a day for 10 days
	Alternative medication	
	Ofloxacin	400 mg per os 2 times a day for 10 days
Complicated forms of urogenital diseases caused by *M. genitalium*	First line treatment	
	Doxycycline monohydrate	100 mg per os 2 times a day for 14—21 days
	Josamycin	500 mg per os 3 times a day for 14—21 days
	Alternative medication	
	Ofloxacin	400 mg per os 2 times a day for 14—21 days
Pregnancy	Josamycin	500 mg per os 3 times a day for 10 days
Children (body weight less than 45 kg	Josamycin	50 mg per kg of body weight per day divided into 3 doses per os for 10 days

The European guidelines for the management of patients with *M. genitalium* infection (2016) include recommendations that three lines of therapy should be used.

As shown in **Table 1**, European guidelines suggest using Pristinamycin as the third line treatment, but this drug has not been used in the Russian Federation so far.

In the Russian Federation, etiotropic treatment regimens for *M. genitalium* infections have been adopted, as shown in **Table 2**.

As can be seen from Table 2, clinical guidelines of the Russian Society of Dermatologists, Venereologists, and Cosmetologists suggest doxycycline and josamycin as the first line treatment, which does not comply with the European guidelines (with respect to doxycycline). Furthermore, the duration of therapy with all antibacterial drugs considerably varies (up to 21 days).

Currently, rapid development of antibiotic resistance of the pathogen is the key problem of treatment of *M. genitalium* infection. Ineffective treatment of *M. genitalium* is due to infection with mutant strains and treatment-induced development of mutations that determine antibiotic resistance.

The efficacy of doxycycline is insufficient for elimination of *M. genitalium* and ranges 30 to 40%, as shown in several controlled studies [42].

Azithromycin used as a single dose of 1 g was previously effective in treatment of *M. genitalium* infection; in the early studies, the efficacy was about 85% [43]. However, further studies (2007 and 2011) showed decrease in efficacy to 40% [44] due to rapidly increasing incidence of resistance to macrolides, most likely due to the widespread use of azithromycin as a single dose of 1 g.

It has been suggested that azithromycin is more likely to cause the development of resistance to macrolides when administered as a single dose of 1 g as compared to protracted treatment [45]. The development of resistance after the protracted treatment with azithromycin was investigated in the observational study [46]. This study demonstrated that none of 77 patients developed resistance after a course of azithromycin. In contrast, 10% of 318 patients treated with 1 g of azithromycin in six studies developed resistance during treatment compared to the protracted therapy. On the other hand, another study showed that protracted treatment with azithromycin leads to resistance, since post-treatment resistance developed in 3 (6.5%) of 46 patients, [47].

Resistance of *M. genitalium* to antibacterial macrolides is associated with A2058, A2059, C2038, and A2062 nucleotide substitutions in the domain V of the 23S rRNA gene (*E. coli*). The study of the nucleotide sequence in the given region of the pathogenic genome makes it possible to identify microorganisms resistant to macrolides [48]. A2062G mutation of the ribosomal gene 23 (different from A2058G/A2059G mutations described for azithromycin) was first described in the Russian Federation for josamycin [49]. *In vitro*, this mutation led to resistance of *M. pneumoniae* to pristinamycin.

The resistance to macrolides demonstrate significant geographical variability. In the regions, where azithromycin was used to treat NGU at a dose of 1 g, resistance usually varies between 30 and 45% [50], and in Green-

land, where azithromycin is widely used to treat infections, almost 100% resistance was reported [51].

Another macrolide, josamycin, is widely used in the Russian Federation to treat *M. genitalium* infection as a first line treatment. In one study, where josamycin was administered at a dose of 500 mg 3 times a day for 10 days, the level of elimination of *M. genitalium* infection was 93.5% in males with urethritis [49].

Moxifloxacin is typically used as a second line treatment. Moxifloxacin has a bactericidal effect and, as a rule, is well tolerated. In early studies, its effectiveness was almost 100% [46]. However, decrease in effectiveness of moxifloxacin treatment was observed primarily in patients in the Asia-Pacific region. Antibacterial activity of fluoroquinolones is associated with inhibitory effect on DNA-gyrase (consisting of two GyrA and two GyrB subunits) and topoisomerase IV (consisting of two ParC and two ParE subunits). It was found that mutations in the *gyrA, gyrB, parC,* and *parE* genes causes development of resistance of the pathogen to a number of antibacterial fluoroquinolones [52]. A significant proportion of *M. genitalium* strains were resistant to both macrolides and fluoroquinolones, so that there were very few available treatment options [53].

Pristinamycin is the only effective antibacterial drug in patients with *M. genitalium* infection resistant to azithromycin, moxifloxacin, and in many cases also to protracted course of doxycycline (100 mg twice a day for 14 days) [53]. In Europe, this drug is registered only in France. It should be used at the maximum recommended dose of 1 g 4 times a day for 10 days; it is the last known active antibacterial therapy. Dose reduction is not recommended, since some strains resistant to many drugs have high minimum inhibitory concentration (MIC) of 0.5 mg, which may lead to ineffective treatment with lower doses [54].

The problem of antibiotic resistance of *M. genitalium*

Rapid development of resistance of *M. genitalium* to various pharmacological groups of antibacterials around the world is one of the key current problems in the treatment of *M. genitalium* infection.

The share of mutant strains is 13.2% with an annual increase by 10—15.4% in France [55]; 31% with increase to 63.6% in Australia [56]; 25% in Singapore [57]. The proportion of mutant strains of *M. genitalium* resistant to macrolides among females involved in commercial sex is 6.2% in Belgium [58].

In Denmark, Norway, and Sweden the resistance of *M. genitalium* to azithromycin and moxifloxacin was studied in 2016. The prevalence of resistant mutations was 41.4% (17.7—56.6%) and 6.6% (4.1—10.2%) for azithromycin and moxifloxacin, respectively. Furthermore, multiple drug resistance was found in these countries (2.7%, 1.1—4.2%) [59].

In Canada, resistance to macrolides and fluoroquinolones reaches 58 and 20%, respectively. In the UK, resistance is 82.4 and 4.9%; in Spain — 35 and 8%, respectively [60].

In 2003, L. Falk reported that 71% of females and 63% of males were newly diagnosed with *M. genitalium* after treatment with doxycycline [61]. The European guidelines for the management of patients with *M. genitalium* infection (2016) state that the efficacy of doxycycline is currently no more than 30% [61].

Multiresistant M. *genitalium* strains has already formed in many countries. The share of these strains is 9.8% in Australia [62] and 30.8% in Japan [63]. There are scarce Russian publications focusing on the detection rate of resistant of *M. genitalium* strains. One research assessed the prevalence and character of *M. genitalium* mutations associated with resistance to macrolides and fluoroquinolones in four Russian cities and in Estonia in 2013—2016. Mutations associated with resistance to macrolides were found in 4.6% of specimens from the Russian Federation (0.7—6.8% in different cities) and in 10% of specimens from Estonia. The frequency of mutations associated with resistance to fluoroquinolones was 6.2% in Russia (2.5—7.6% in different cities) and 5% in Estonia. About 1% of specimens in both countries contained mutations to both macrolides and fluoroquinolones [64].

Conclusions

The development of new methods for management of patients with *M. genitalium* infection based on the study of genetic mutation spectrum of the pathogen and comparing to clinical data is currently one of the most pressing problems of dermatovenerology and related specialties. Much attention is given to this problem at the clinical department of dermatovenerology and cosmetology of the Moscow Scientific and Practical Center for Dermatovenereology and Cosmetology of the Moscow Healthcare Department.

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