Mycoplasma genitalium – a better known microorganism and its implications in an old gynecological pathology

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Abstract

Mycoplasma genitalium belongs to the Mollicute class, represented by the smallest microorganisms which can live independently without a cell wall. From the same class, also involved in urogenital system pathogenesis, we mention Mycoplasma hominis and ureaplasmas, like Urealiticum or Parvum. Mycoplasma genitalium infection is found in 1-3.3% of individuals amongst the general population, but there is a higher prevalence among patients with nongonococcal urethritis (10-35%) or in patients with chronic cervicitis and pelvic inflammatory disease (12-28%). The recurrence of the infection and its chronic evolution yield an important practical importance. The main risk factors associated with Mycoplasma genitalium are represented by: age under 20 years old, more than two past sexual partners, and smoking. Mycoplasma genitalium is sensible to tetracyclines, macrolides and fluoroquinolones. Nevertheless, it seems that the microorganism has a great capacity to quickly acquire antibiotic resistance. The risk of recurrence of the Mycoplasma genitalium infection is high, both in women and men. The repeated urinary symptoms in men and also the urinary or genital symptoms in women are suggestive. The treatment must be resumed by choosing the optimal antibiotic. It is imperative that the sexual partner be tested and treated. Finally, it is important to check the cure of the infection. The risks of recurrence and/or persistence consists in the chronic pelvic inflammatory disease (CPID) with endometritis and chronic salpingitis. CPID can thus lead to infertility, due to the endocervical, endometrial and tubal mucosa injury.

Keywords: *recurrent genital infections, Mycoplasma genitalium*

Rezumat

Mycoplasma genitalium aparține clasei Mollicute, cele mai mici microorganisme fără perete celular propriu, care pot trăi liber. Din aceeași clasă mai sunt implicate în patogenia aparatului urogenital Mycoplasma hominis și ureaplasmele (Urealiticum, Parvum). În populația generală se întâlnește la 1-3,3% dintre indivizi (femei și bărbați), dar prevalența este crescută la pacienții cu uretrite nongonococice (10-35%) sau la pacientele cu cervicite cronice și boală inflamatorie pelviană (12-28%). De mare importanță practică sunt recurența infecției și cronicizarea ei. Sunt considerați factori de risc pentru infecția cu Mycoplasma genitalium: vârsta (sub 20 de ani), mai mult de doi parteneri sexuali, fumatul. Tabloul clinic este sugestiv pentru cervicită cronică, boală inflamatorie pelviană sau sindrom algic pelvian. Antibioticele la care Mycoplasma genitalium este sensibilă sunt tetraciclinele, macrolidele și fluorochinolonele. S-a observat că microorganismul are o capacitate foarte mare de a dobândi rapid rezistență la antibiotice. Atât la bărbați, cât și la femei, riscul recurenței unei infecții cu Mycoplasma genitalium este mare. Sugestive sunt reapariția simptomelor urinare la bărbați și a celor urinare și genitale la femei. Tratamentul trebuie reluat foarte corect, cu alegerea antibioticului potrivit, pentru o durată suficientă, cu tratarea obligatorie a partenerului și verificarea negativării infecției. Riscurile recurenței și/sau persistenței sunt reprezentate de boala inflamatorie pelviană conică, cu endometrită și salpingită cronică, iar la distanță, cu infertilitate (prin afectarea mucoaselor – endocervicală, endometrială și endosalpingiană).

Cuvinte-cheie: *Mycoplasma genitalium, infecții genitale recurente*

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Mycoplasma genitalium – un microorganism ceva mai bine cunoscut pentru o patologie ginecologică veche

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Introduction

Most of the examinations in the gynecology office are requested by patients who have suggestive symptoms of pelvic pain syndromes, accompanied or not by other cardinal symptoms in gynecology, such as bleeding and leukorrhea. For many patients, this is not the first episode of this kind. Also, there are some patients who have repeated episodes of vaginal bleeding or pelvic pain, which suggest the chronicity of some diseases. Germs with sexual transmission are the main ones involved in the etiology of these types of diseases. The following are frequently encountered (isolated or

associated): gonococcus (*Neisseria gonorrhoeae*), *Chlamydia trachomatis*, *Mycoplasma* (*hominis*, *genitalium*) and *Ureaplasma* (*urealiticum*, *parvum*), *Trichomonas vaginalis* or non-specific germs. Among them, *Mycoplasma genitalium* is interesting, because it seems to be responsible for the chronic evolution of inflammatory diseases of the genitourinary system.

Materials and method

We present an update of the data based on *Mycoplasma genitalium* infections, as it results from the literature of the moment, insisting on the immunopathogenic mechanisms that allow us to understand the implications of this germ in gynecological pathology, as we can observe them in current practice. The obstetric implications of *Mycoplasma genitalium* infection are not the subject of this material.

Mycoplasma genitalium belongs to a germ class named *Mollicute*, the family *Mycoplasmataceae*, represented by the smallest microorganisms without their own cell wall which can live freely. *Mycoplasma hominis* and ureaplasmas (*U. urealiticum*, *U. parvum*) are also involved in the pathogenesis of the urogenital tract. *Mycoplasma genitalium* was first described in 1980, when it was isolated from the urethral secretion of two men with nongonococcal urethritis[1]. It was grown with much difficulty in the laboratory (because it grows very slow and with difficulty on microbiological cultures). Until the early 1990s, when this microorganism could be identified using nuclear amplification methods, its involvement in inflammatory diseases of the urogenital tract could not be established.

Mycoplasma genitalium does not have its own bacterial wall and therefore cannot be identified by Gram staining. It is very small (0.6/0.3 micrometers). It needs anaerobic nitrogen atmosphere in the culture medium, with 5% CO_2 and a temperature of 37 degrees Celsius. Bacterial colonies have a characteristic known as "egg-eye" appearance, which have a more colorful and dense center and a paler shade at periphery[2]. Its genome has only 580 kilobases, being the second bacterial genome described in the literature (1995). It consists of a circular, double-stranded DNA that appears to hold all the genetic information, because no plasmids or extrachromosomal DNA have been described[3]. Having adaptively such a small genome, *Mycoplasma* obviously has important metabolic restrictions (it does not have almost all the enzymes which are necessary for the synthesis of amino acids or fatty acids). So, it is clearly dependent on its host and also creates favorable conditions to survive in the infected epithelium.

Mycoplasma genitalium infection occurs in 1-3.3% of the general population (women and men)[4], but the prevalence is higher in patients with nongonococcal urethritis (10-35%)[2] or in those with chronic cervicitis and pelvic inflammatory disease (12-28%)[4]. The incidence is also significant among infertile couples. Of great practical importance are the recurrence and the chronicity of the infection. This phenomenon has two explanations: on the one hand, the resistance that the germ quickly acquires to antibiotics and, on the other hand, the way it stimulates the local inflammatory mechanism.

Based on the concordance of the DNAs of the germs present in both sexual partners, the following transmission routes are described: genital-genital; genital-anorectal; genital-pharyngeal (probably very low, because the portage is low at the oropharyngeal level); vertical transmission from mother to child (less researched, but the presence of *Mycoplasma genitalium* was demonstrated in newborns, in the respiratory tract). *Mycoplasma genitalium* is considered less contagious than *Chlamydia trachomatis*. Also, the maximum incidence of age is slightly higher than that of *Chlamydia* (on average by five years, around 20-24 years old).

The risk factors for acquiring *Mycoplasma genitalium* are: age (under 20 years), more than two sexual partners and smoking. The infection is more common in HIV-positive patients. Co-infections with *Chlamydia trachomatis*, gonococcus or both are described.

Mycoplasma genitalium infection has several immunopathogenic characteristics that must be understood. Thus, when we refer to acute infection, *Mycoplasma genitalium* attaches mainly to the endocervical epithelium, through mucin-binding proteins, which are components of mucous secretions that exist at this level[5]. The attachment occurs through one of the ends of the bacterium, provided with a special attachment device, consisting of a very complex protein structure (demonstrated electromicroscopically)[2]. This attachment occurs extremely quickly, followed by an equally rapid epithelial penetration, which appears to bypass the acute phase immunological mechanisms of the epithelial surface. At this level, there is a significant inflammatory response, represented by a secretion of some proinflammatory cytokines and chemokines (interleukins IL 6, IL 7, IL 8, monocyte chemotactic protein 1, stimulator of granulocyte-macrophage colonies etc.). This type of response determines a massive recruitment of leukocytes and practically amplifies the local immune response (as results from experimental studies on female chimpanzees inoculated with *Mycoplasma genitalium*)[6]. This phenomenon is indirectly demonstrated on women, by detecting a large number of leukocytes on smears secreted by those infected with *Mycoplasma genitalium* (we easily recognize the pattern: a patient with clinical cervicitis, but with negative cultures and cervical cytological smear with very numerous polymorphonuclear cells). *Mycoplasma genitalium* can cause tubal cilia damage, but to a significantly lower extent than *Chlamydia trachomatis*.

The infection with *Mycoplasma genitalium* frequently persists, turning into a chronic infection, having a risk to ascend in the upper genital tract (although the mechanism of this ascension is not well defined). The incomplete or inappropriate antibiotic treatments contribute to this. Massively recruited polymorphonuclear cells at the inoculation site release hydrolytic enzymes

and oxidizing agents that cause tissue damage, as well as cytokines and chemokines that will activate the local inflammatory response[7]. Thus, this infection looks like a smoldering fire, and the consequences are significant, successively being affected the endocervical, endometrial and tubal mucous membranes.

Moreover, *Mycoplasma genitalium* appears to be able to "escape" from destruction by internalizing vacuoles in epithelial cells (escaping from direct phagocytosis) and by permanently modifying its surface antigens.

The clinical manifestations of *Mycoplasma genitalium* infection are diverse. Frequently, cervicitis can be asymptomatic for the patient, being discovered at a careful gynecological consultation. Most often patients have leukorrhea (yellowing), dysuria, polakiuria or different levels of pelvic pain (spontaneous, during sexual intercourse or after sexual contact). Not infrequently, these symptoms are recurrent, although the patients have tried multiple treatments.

At the clinical examination, yellowish, mucous, mucopurulent leukorrhea is observed in the vagina. Rarely, this leukorrhea can be frankly purulent. The intravaginal swab test is positive (the swab used for the test, being inserted into the endocervix, becomes yellowish) (Figure 1). The cervix bleeds slightly when is touched with the valve or when we use the swab for the test[8]. Most of the time, however, the only significant aspect is the opaque cervical glare.

During bimanual vaginal examination, we observe sensitivity to the mobilization of the cervix, the adnexa more or less palpable and sensitive. Numerous polymorphonuclear leukocytes are observed on the vaginal and cervical smear. The cultures for the germs which are usually tested are negative. Urine cultures are repeatedly sterile.

When pelvic inflammatory disease occurs, the patient primarily has pelvic pain of different levels of intensity, with or without extension of the pain to the thighs or sacrum. Most often, the pain worsens after exposure to cold or after sexual intercourse. Many patients have an important level of dyspareunia of different intensities. There are some other signs for which the patient come to the gynecological examination: small intermenstrual bleeding, small postcoital bleeding, and less often meno- or menometrorrhagia[9]. The clinical signs are not very pronounced, the pelvic pain is not very strong, and the fever is not very high[10]. The anamnesis can detect urinary symptoms (dysuria, polakiuria, for which the patient has had repeated treatments without a long-time success). Frequently, the partner had or has a urethritis or, most frequently, a recurrent urinary symptomatology.

Figure 1. *The tampon sign*

Rectal or pharyngeal infections are usually asymptomatic or the symptoms are nonspecific. Some patients may have sexually acquired reactive arthritis (joint pain and stiffness), but also a possible adult conjunctivitis may occur in this context.

There is currently no validated and approved biological test for the diagnosis of *Mycoplasma genitalium* infection in either Europe or the United States of America. Commercial tests detect *Mycoplasma genitalium* using a nucleic acid amplification technique, usually chain polymerization reaction (PCR)[11]. We must pay attention to the transport medium (media for *Chlamydia trachomatis* lyses *Mycoplasma genitalium*).

In Romania, there are currently individual kits for the detection of *Mycoplasma genitalium* or panel tests for seven, eight or ten germs, which also include *Mycoplasma genitalium*.

The sampling is done as follows.

a. In women: vaginal and endocervical sampling to increase the sensitivity of the test. The collection of 10 ml of urine from the first stream is also discussed (without a local toilet, collected after at least two hours, time when the patient does not urinate)

b. In men: from the first stream of urine, with the same recommendations as above.

As germ resistance to macrolides is currently recognized in Europe, field authorities recommend that laboratories must test germs for mutations that allow antibiotic resistance (for macrolides and moxifloxacin) [12]. No serological tests are currently available for Mycoplasma genitalium. It is considered that patients who are positive for *Mycoplasma genitalium* should also be tested for other sexually transmitted diseases (hence the practical usefulness of test panels, but which is significantly more expensive).

The therapeutic protocols take into account that the antibiotics to which *Mycoplasma genitalium* is sensitive are tetracyclines, macrolides and fluoroquinolones. However, it seems that the microorganism has a very high capacity to rapidly acquire antibiotic resistance[12].

We present the therapeutic schemes proposed by the Guide of the European Dermatology Forum in 2016[13] (Table 1).

If the patient has a recurrency after being treated with Azithromycin, Josamycin or Moxifloxacin, the following treatments are suggested: Pristinamycin 1g four times a day, for ten days or doxicillin 100 mg, two

Table 1 Treatment schemes for *Mycoplasma genitalium* infection

Macrolides	
Azithromycin	1 g on the first day, then 200 mg for another five days or 500 mg daily for seven days
Josamycin	500 mg three times a day, 10 days
Fluoroquinolones	
Moxifloxacin	400 mg/day, 7-10 days

Table 2 Treatment scheme for recurrencies in infections with *Mycoplasma genitalium*

Pristinamycin	1g four times a day, ten days
Doxicillin	200 mg/day, ten days, although the cure rate is low, 30-40%

times a day, for ten days (although the cure rate is low (30-40%) (Table 2).

The empirical treatment schedules are also proposed, as long as the involvement of *Mycoplasma genitalium* is suspected:

- in acute pelvic inflammatory disease, it is recommended to start the treatment with moxifloxacin for 14 days;
- in cervicitis or urethritis, it is recommended to start the treatment with azithromycin for seven days.

The treatment of the partner is mandatory. A biological sample is taken ideally before starting the treatment. Susceptible partners are those with whom the patient has had sexual intercourse in the last six months.

Microbiological tests which suggest that the infection becomes negative should be done after more than three weeks from the end of treatment. Some studies even recommend retesting after the first negative one.

In both men and women, the risk of recurrence of *Mycoplasma genitalium* infection is high. The recurrence of urinary symptoms in men and urinary and genital symptoms in women are suggestive. The treatment must be very correctly applied, by choosing the right antibiotic therapy, administrated for an appropriate period of time. It is mandatory to start the treatment of the sexual partner and also we must check if the infection resolves after treatment.

The risks of recurrence and/or persistence are represented by chronic pelvic inflammatory disease, with chronic endometritis and salpingitis, and after a while, this can lead to infertility (affecting the endocervical, endometrial and tubal mucosa).

Discussion

One of the current concerns is the time when we should actively test our patients for *Mycoplasma genitalium*. According to the European Dermatology Forum Guide (2016, modified in 2018), the following situations are acceptable.

a. In women: clinical signs of mucopurulent cervicitis (positive endocervical tampon sign), leukorrhea described by patients who have some risk factors for sexually transmitted diseases, intermenstrual or postcoital bleeding, pelvic pain syndromes, pelvic inflammatory disease, tests of the people who have an high-risk sexual behavior (more than three sexual partners in the last year), test of the people who have direct contact with other people who are known to have *Mycoplasma genitalium* infection and, also, before any maneuver that creates some kind of discontinuities in the endocervical barrier (abortion, curettage or endometrial aspiration, conservative interventions on the cervix etc.).

b. In men: symptoms or signs suggestive of acute urethritis or orchiepididymitis.

Another current question is how can we increase the cure rate in *Mycoplasma genitalium* infection. The cure rate can be increased taking into account the particularities of this infection, especially the important inflammatory reaction, which allows the chronicity and rapidly acquired antibiotic resistance. The high level of suspicion in the clinical situations described above, combined with the right choice of the antibiotic treatment for *Mycoplasma genitalium* – azithromycin or moxifloxacin[14] and, surely, the treatment of the partner, should significantly increase the cure rate.

It is very important to discuss about the long-term implications of *Mycoplasma genitalium* infection[15]. Because we frequently examine patients with chronic cervicitis or chronic inflammatory disease and its sequelae (the first place being represented by infertility), people who have usually done more treatments and had more recurrences, the diagnostic and therapeutic approach must be adapted to the patient. The infections either had a subclinical evolution or they were not recognized.

Although it involves a significant increase in costs, we should ideally be able to do a laboratory test for *Mycoplasma genitalium*[17]. If this is not possible, we will start with an empirical treatment, reviewing past treatments at the same time and, finally, choosing a macrolide or a fluoroquinolone. The treatment must be done for the right period of time, as recommended, and we will also prescribe a treatment for the partner. Sexual abstinence or condom use is recommended until the infection is negative in both partners[18]. If retesting is not possible, we will check the healing by clinical tests (endocervical tampon test) and by the examinations of the cervical smear (decrease until the disappearance of polymorphonuclear cells on the smear).

Conclusions

All sexually transmitted diseases are relevant because of the suffering and sequelae they can cause[19]. In case of *Mycoplasma genitalium* infection, the keywords are represented by the atypical clinical picture (low genital infection, pelvic inflammatory disease or asymptomatic disease), the possibility of recurrence and chronic infection influencing the local immune response. It is mandatory to diagnose and treat correctly the infection from the beginning. The patients must be fully and correctly informed about the risks of infection and the limits of treatment[20]. ■

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