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Prevalence and Antibiotic Susceptibility of *Ureaplasma spp.* and *Mycoplasma hominis* Strains in Sexually Active Women in Romania

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Abstract

Mycoplasma hominis and *Ureaplasma* spp. are frequently found in the genital tract, especially in sexually active women, pregnant or not, with a negative impact on health and outcome of pregnancy. The retrospective study investigates the prevalence of colonization/infection with genital mycoplasmas in women and the antibiotic susceptibility profile of the isolated strains. From August 2011 till July 2017, 931 endo-cervical samples were analyzed. Mycoplasma IST2 kit (Biomerieux) was used for culture, identification, indicative enumeration and antibiotic susceptibility testing. Culture was positive in 38.5% of the samples. *Ureaplasma* predominated, *Mycoplasma* being detected mostly in association with *Ureaplasma*, seldom alone. Overall, the level of resistance to quinolones was high (77% for ciprofloxacin, 55% for ofloxacin), whilst that of resistance to tetracyclines only started to rise. Some *Ureaplasma* strains showed resistance to three classes of antibiotics. For erythromycin, a particular trend was noticed, with a drop of resistance level during the study, but with recent re-emergence of resistant *Ureaplasma* strains. Pristinamicin resistance was not encountered. Tetracyclines are still the antibiotics of choice for these infections. As the rising trend of resistance to several classes of antibiotics might become problematic over the next decades, antibiotic susceptibility of the strains should be assessed prior to the initiation of treatment.

Key words. *Ureaplasma* spp., *Mycoplasma hominis*, screening, colonization, infection, antibiotic susceptibility.

Резюме

Mycoplasma hominis и *Ureaplasma* spp., които са често срещани в гениталния тракт, особено при сексуално активни жени (бременни или не), оказват отрицателно въздействие върху здравето и изхода от бременността. Целта на настоящото ретроспективното проучване е да се установи колонизацията/инфекцията с генитални микоплазми при жените и профила на антибиотична чувствителност на изолираните щамове. От август 2011 г. до юли 2017 г. са анализирани 931 ендоцервикални проби. За културане, идентификация, индикативно изброяване и тестване за чувствителност към антибиотици се използва Mycoplasma IST2 кит (Biomerieux). Резултатите показват, че културата е установена в 38.5% от пробите. Преобладa уреаплазмата, а *Mycoplasma* се открива предимно в комбинация с *Ureaplasma* и много рядко самостоятелно. Нивото на резистентност към хинолони е високо (77% при ципрофлоксацин, 55% при офлоксацин), докато резистентността към тетрациклини едва сега започва да се повишава. Някои щамове на *Ureaplasma* показват резистентност към три класа антибиотици. За еритромицин се установява особена тенденция - спад на нивото на резистентност по време на проучването, но с последваща повторна поява на резистентни щамове на *Ureaplasma*. Резистентността към прищинамицин не се наблюдава. Тетрациклините са все още предпочитаните антибиотици за тези инфекции. Тъй като нарастващата тенденция на резистентност към няколко класа антибиотици може да стане проблематична през следващите десетилетия, антибиотичната чувствителност на щамовете трябва да бъде оценена преди започване на лечението.

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Introduction

Mycoplasmas represent a group of microorganisms commonly found in the genital tract of women. Worldwide, detection rate of *Ureaplasma* spp. (UU) in the human genital tract might reach 60-80% in sexually active women, while colonization figures for *Mycoplasma hominis* (MH) range between 20 and 30% (Bayraktar *et al*., 2010). There is still controversy regarding the association of genital mycoplasmas with bacterial vaginosis, some investigators claiming the existence of a relationship between the two (Keane *et al*., 2000), other investigators being more skeptic (Arya *et al*., 2001). Both UU and MH are sexually transmitted bacterial pathogens, undoubtedly involved in impairment of reproductive status, although numerous and often contradictory papers concerning their real pathogenic potential have been published in the last years. These microorganisms, especially UU, have been associated with various pathological conditions and intrauterine infections, including pyelonephritis, pelvic inflammatory disease or endometritis, leading to important complications, like infertility, lower pregnancy rates after *in vitro* fertilization, chorioamnionitis, spontaneous abortion, stillbirth, preterm birth, low birth weight and perinatal mortality, postpartum fever (Daxboeck *et al*., 2005, Pararas *et al*., 2006). MH is involved in the aetiology of salpingitis and pelvic inflammatory disease, but its occurrence in sexually active population is lower than that of UU (Waites *et al*., 2009).

The fact that mycoplasmas do not have a cell wall provides them with a unique pattern of susceptibility to antimicrobial agents. Antibacterial agents like penicillin and cephalosporins do not act against these microorganisms, due to lack of target. MH strains are naturally resistant to erythromycine. Resistance to quinolones or tetracyclines has been documented in clinical isolates worldwide, antibiotic resistance of individual strains being heterogeneous.

The study is a retrospective one, concerning UU and MH colonization and infection and the antibiotic susceptibility of the isolated strains in the sexually active female population, symptomatic or not, attending a laboratory in Bucharest, Romania.

Material and Methods

From August 2011 till July 2017, 931 endo-cervical samples were analyzed in the Laboratory of Medical Analysis in the Cantacuzino Institute in Bucharest, Romania. The samples were collected from sexually active women, aged 17-62, who were either asymptomatic (presenting to the laboratory for screening), or symptomatic, non-pregnant or pregnant, residing, in most of the cases, in Bucharest and surroundings. We excluded from the study samples belonging to patients who attended in order to check for treatment efficiency after having been previously diagnosed and treated.

Mycoplasma IST2 kit (Biomérieux) was used for culture, identification, indicative enumeration and antibiotic susceptibility testing. The test can detect the presence of *Ureaplasma urealyticum* and *Ureaplasma parvum* (without making a distinction between the two) and *M. hominis*. The culture medium used was adapted for the optimal growth of mycoplasmas in terms of pH, substrates and growth factors, including specific substances (urea for UU and arginine for MH) and an indicator (phenol red) that allows in the case of positive cultures the display of a color change in the stock, related to an increase in pH. The test provides information about the amount of germs present in the sample, consistent with colonization if the bacterial count is less than 10^4 colony forming units (CFU) in the specimen, or infection, if equal to or greater than this figure. The susceptibility testing was performed for nine antibiotics: macrolides (azithromycin, erythromycin, clarithromycin and josamycin), fluoroquinolones (ciprofloxacin and ofloxacin), tetracyclines (doxycycline and tetracycline), and a streptogramin: pristinamycin. The endo-cervical cotton swab was processed as indicated by the manufacturer.

Results and Discussions

Out of the 931 samples collected, 358 (38.5%) were positive either for UU or for MH or for both. The prevalence of genital colonization or infection due to UU was considerably higher as compared to MH. MH was mostly detected as colonizer, while indicative enumeration pointed to UU as mostly involved in infection (Fig. 1, 2 and 3).

Regarding antibiotic susceptibility, it is important to mention that colonization strains showed resistance to a lesser extent than strains involved in infection. Overall, the highest level of resistance was to quinolones (77% for ciprofloxacin, 55% for ofloxacin). We did not encounter strains resistant to ofloxacin without showing as well resistance to ciprofloxacin. Resistance to erythromycin was rather high, as well (around 60%) and was not solely relying on MH strains, which are naturally resistant to this macrolide. A lot of UU strains were resistant to erythro-

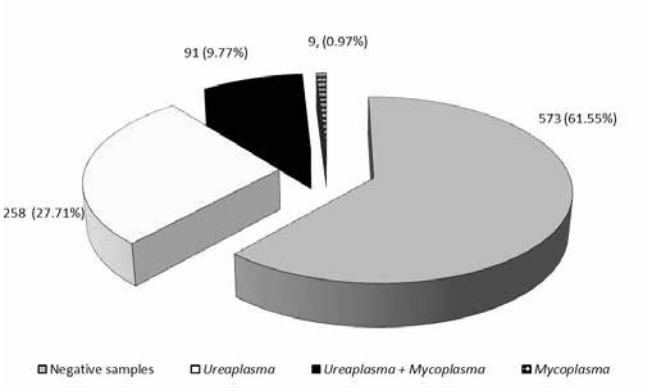

Fig. 1. Distribution of cases

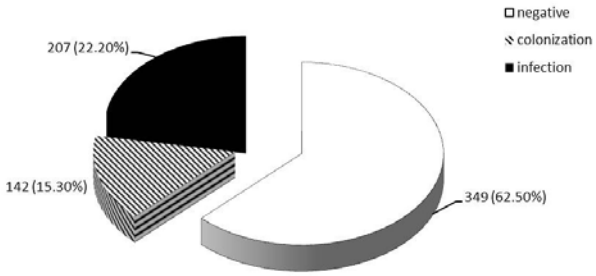

Fig. 2. *Ureaplasma* spp. – colonization versus infection

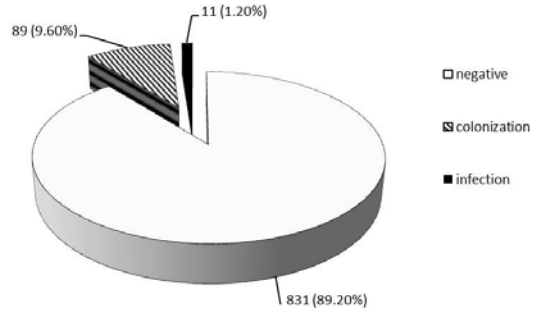

Fig. 3. *M. hominis* – colonization versus infection

mycin and had an interesting pattern of evolution: we registered erythromycin-resistant UU strains in 2011-2013, followed by a drop of resistance level, until recently, in 2017, when resistance to this macrolide re-emerged. The fact that we isolated many strains with intermediate resistance to azythromycin and clarithromycin might be indicative of a rising tendency. The level of resistance to tetracyclines was very low, but started to rise. When analyzing samples in which both UU and MH were detected, extrapolation of data allows us to presume that resistance to tetracycline is the apanage of UU strains. Some UU strains showed multiple resistance (quinolones, macrolides, tetracyclines). Pristinamicin resistance was not encountered (Fig. 4, Tables 1 and 2).

Literature does not abound in studies referring to the isolation of mycoplasmas and their antibiotic susceptibility profile, this being due to the difficulty in culturing those microorganisms and to the lack of a standardized method for the interpretation of the resistance profile. EUCAST regulations do not include standards for mycoplasmas.

The methods available for the diagnosis of mycoplasma infections rely mainly on commercial kits based on substrates used by these germs, with a colour reaction providing the positive result for germ growth. Molecular techniques of detection are available, but they are still very expensive for most of the facilities and for the patients (in Romania the state health insurance does not cover detection of these pathogens). The choice of the *Mycoplasma* IST2 kit did not rely on its popularity; we have previously tested several such commercial kits and the results pointed out that this was the most reliable in terms of accuracy, sensitivity and specificity (Năşcuţiu, unpublished data). The test is easy to perform, yet it requires rigour, attention and careful interpretation of results. A recent Polish study showed that although a negative result obtained with the use of the *Mycoplasma* IST2 kit may be considered reliable, the samples positive

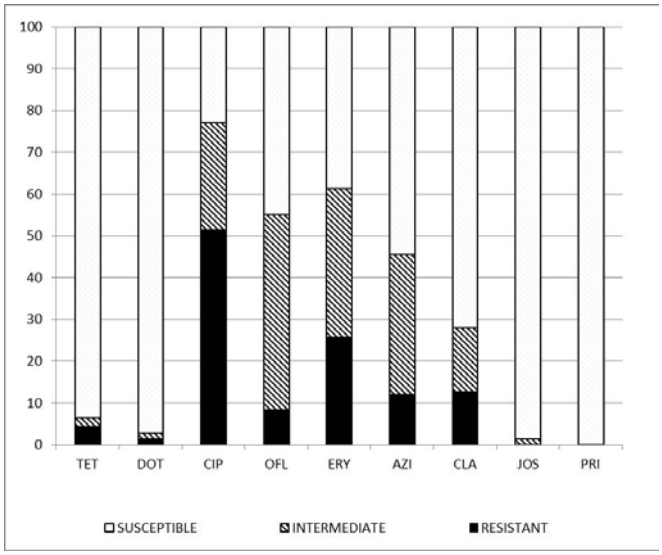

Fig. 4. Global antibiotic susceptibility profile
TET - tetracycline, DOT - doxycycline, CIP - ciprofloxacin, OFL - ofloxacin, ERY - erythromycin, AZY - azythromycin, CLA - clarithromycin, JOS - josamycin, PRI - pristinamycin

Table 1. Antibiotic susceptibility profiles of *Ureaplasma* spp. strains

		Ureaplasma - colonization			*Ureaplasma* - infection		
		UU < 10^4 MH -	UU < 10^4 MH < 10^4	UU < 10^4 MH > 10^4	UU > 10^4 MH -	UU > 10^4 MH < 10^4	UU > 10^4 MH > 10^4
TET	S	116	15	4	130	56	5
	I	1	0	0	3	3	0
	R	3	3	0	5	5	0
DOT	S	117	17	4	134	62	5
	I	3	1	0	1	0	0
	R	0	0	0	3	2	0
CIP	S	40	15	3	14	2	0
	I	38	3	0	43	7	0
	R	42	0	1	81	55	5
OFL	S	65	2	3	30	54	0
	I	43	13	1	97	8	3
	R	12	3	0	11	2	2
ERY	S	68	1	0	70	0	0
	I	25	3	0	68	31	0
	R	27	14	4	0	33	5
AZY	S	106	2	0	80	7	0
	I	14	5	0	57	40	3
	R	0	11	4	1	17	2
CLA	S	124	4	3	112	25	0
	I	3	2	0	26	22	2
	R	3	12	1	0	17	3
JOS	S	119	18	4	136	63	4
	I	1	0	0	2	1	1
	R	0	0	0	0	0	0
PRI	S	120	18	4	138	64	5
	R	0	0	0	0	0	0

UU - *Ureaplasma* spp, MH - *Mycoplasma hominis*

S - sensitive, I - intermediate, R – resistant

DOT - doxycycline, TET - tetracycline, CIP - ciprofloxacin, OFL - ofloxacin, ERY - erythromycin, AZY - azythromycin, CLA - clarithromycin, JOS - josamycin, PRI - pristinamycin

Table 2. Antibiotic susceptibility profiles of *Mycoplasma* spp. strains

		Mycoplasma colonization			*Mycoplasma* infection		
		MH < 10^4 UU -	MH < 10^4 UU < 10^4	MH < 10^4 UU > 10^4	MH > 10^4 UU -	MH > 10^4 UU < 10^4	MH > 10^4 UU > 10^4
DOT	S	7	17	62	2	4	5
	I	0	1	0	0	0	0
	R	0	0	2	0	0	0
TET	S	7	15	56	2	4	5
	I	0	0	3	0	0	0
	R	0	3	5	0	0	0
CIP	S	6	15	2	2	3	0
	I	1	3	7	0	0	0
	R	0	0	55	0	1	5
OFL	S	5	2	54	2	3	0
	I	2	13	8	0	1	3
	R	0	3	2	0	0	2
ERY	S	0	1	0	0	0	0
	I	0	3	31	0	0	0
	R	7	14	33	2	4	5
AZY	S	0	2	7	0	0	0
	I	1	5	40	0	0	3
	R	6	11	17	2	4	2
CLA	S	0	4	25	0	3	0
	I	0	2	22	0	0	2
	R	7	12	17	2	1	3
JOS	S	7	18	63	2	4	4
	I	0	0	1	0	0	1
	R	0	0	0	0	0	0
PRI	S	7	18	64	2	4	5
	R	0	0	0	0	0	0

MH - *Mycoplasma hominis*, UU - *Ureaplasma* spp.
S - sensitive, I - intermediate, R – resistant
DOT - doxycycline, TET - tetracycline, CIP - ciprofloxacin, OFL - ofloxacin, ERY - erythromycin, AZY - azythromycin, CLA - clarithromycin, JOS - josamycin, PRI - pristinamycin

for MH should be confirmed by another method, e.g. cultures on PPLO media ("golden standard") or PCR (Biernat-Sudolska *et al*., 2013). We have been confronted with several such circumstances when the test was positive, especially when the culture of the sample on blood-agar or selective media for Gram-negative germs proved growth of the latter. This can be explained by the fact that, despite the manufacturer's use of factors that selectively inhibit growth of fungi, Gram-positive and, especially, Gram-negative bacteria, their presence cannot be completely eliminated. Bacteria that produce urease, or that are capable of arginine degradation, if present in the sample, might be a cause of false-positive results. In this case, when lacking detection alternative, a thorough analysis of the antibiotic susceptibility profile might be of help. A Greek study suggested that false positive results for MH are to be suspected when UU also tests positive, with titers above 10^4 CFU in the specimen, and global resistance to macrolides is intermediate (Kechagia *et al*., 2008). Our observations are consistent with this study.

With respect to antibiotic resistance profiling of the strains, if these commercial tests are excellent for clinical purposes, difficulties in interpreting antibiotic susceptibility results can arise when confronted with UU and MH co-carriage, carriage-infection or co-infection. In these cases the test cannot provide separate accurate information regarding the susceptibility of each strain involved, only an approximate extrapolation being made.

Studies performed so far have shown diversity of antibiotic susceptibility patterns according to the geographical area. Nevertheless, a geographical pattern cannot be always proved. We believe that in the distinct resistance profiles from different parts of the world, geography is not as much involved as are the local antibiotic use regulations. Sustaining our assertion is for instance a very recent study (Skiljevic *et al*., 2016) from a neighbouring country - Serbia - which showed that among MH strains the drug resistance rate was 100% to erythromycin, tetracycline, clarithromycin and UU strains were highly resistant to clarithromycin (94.6%), tetracycline (86.5%), ciprofloxacin (83.8%) and erythromycin (83.8%). Our studies were more optimistic with respect to MH resistance to clarithromycin, whereas tetracycline resistance was exceptional. Erythromycin resistance in UU strains did not exceed 50% in our study.

Mycoplasmas are normally susceptible to antibiotics that inhibit protein synthesis. MH is intrinsically resistant to erythromycin, which was a characteristic we confirmed by our results. We found in our studies UU strains simultaneously resistant to several classes of antibiotics, which might support the assertion of our Hungarian colleagues that "ex juvantibus therapies may select cross-resistant strains" (Farkas *et al*., 2011). Similar figures as ours for the resistance of UU to erythromycin were reported in Egypt - 55% (Safaa *et al*., 2016); meanwhile, a South African study reported a discouraging 89% resistance (Redelinghuis *et al*., 2014). The recently rising trend of clarythromycin resistance of the UU strains might be explained by the fact that it has been increasingly used as a treatment tool as it has been demonstrated that it is the best medication for treating infections with biofilm-producing *U. urealyticum* strains, due to its capacity to penetrate the biofilm and/or to inhibit its formation.

With respect to UU resistance to tetracycline, different susceptibility rates have been encountered in various locations and in different types of populations studied. In Germany, 20 years ago, a study reported that all UU strains were susceptible to doxycycline (Ullmann *et al*., 1999), while another study (Abale-Horn *et al*., 1997) detected a substantial resistance to doxycycline (up to 55%) as well as to the older fluoroquinolones (42% for ciprofloxacin and 61% for ofloxacin), with all isolates being susceptible to erythromycin and clarithromycin. Consistent with the latter, a recent South African study detected tetracycline resistance in 73% of UU strains (Redelinghuys *et al*., 2014). On the other hand, high UU susceptibility rates to doxycycline and tetracycline were documented in Croatia (Marekovic *et al*., 2007), Hungary (Ponyai *et al*., 2013), Greece (Kechagia *et al*., 2008), Germany (Krausse *et al*., 2010), Italy (Leli *et al*., 2012), Turkey (Aydin *et al*., 2005; Bayraktar *et al*., 2010), Israel (Samra *et al*., 2011), Chile (Martinez *et al*., 2001) and Korea (Koh *et al*., 2009). A German 20-year survey pointed out that MH strains are more likely to be resistant to tetracyclines than UU strains (Krausse *et al*., 2010). Our study's results disagree with these findings. Studies have been as well performed with respect to the possible effect of the tetracycline-susceptibility status of ureaplasmas on their susceptibility to macrolides and fluoroquinolones. The comparable activity of newer fluoroquinolones (grepafloxacin, trovafloxacin) against ureaplasmas regardless of their resistance status to tetracyclines has also been documented (Duffy *et al*., 2000).

There seems to be a predominant pattern with much higher resistance rates to macrolides and flu-

oroquinolones than to tetracyclines, as shown by a Chinese study performed between 1999 and 2004: up to 88.8% resistance to ciprofloxacin, against only 9.8% resistance to tetracycline and 4.4% to doxycycline, respectively, results being motivated by the widespread use of fluoroquinolones and rare use of tetracyclines in China (Xie *et al*., 2006). High resistance rates to fluoroquinolones and erythromycin were also reported from Turkey: ciprofloxacin 40.5%, ofloxacin 58.4%, erythromycin 54.0%, while resistance to tetracycline was 13.5% and to doxycycline 1.6% (Karabay *et al*., 2006). High rates of fluoroquinolone resistance have also been described in Mexico (Fagundo-Sierra *et al*., 2006). In Italy, 66.4% of UU isolates were resistant to ciprofloxacin, whereas 27.6% were resistant to ofloxacin (Leli *et al*., 2012), consistent with our results, at least for ciprofloxacin resistance. Yet, in the same Italian strains, no resistance was found to azithromycin, or erythromycine, while 66.7% of the MH strains were resistant to azythromycin, but none to ciprofloxacin, ofloxacin, doxycycline, josamycin or pristinamycin. Surprisingly, a very recent Egyptian study (Safaa *et al*., 2016) found sensitivity rates of 90–95% for the UU strains tested against quinolones.

Published data available so far from Romania (from Iaşi, the Northern part of the country) show that MH is more likely to be resistant than UU to ciprofloxacin (75% and 53.76%, respectively), the resistance rate being however very high for both species compared with similar studies (Mareş *et al*., 2011). Our study could not support this assertion, the great majority of MH strains being still susceptible to ciprofloxacin.

Resistance to "old" fluoroquinolones seems to be high in many studies performed worldwide. An explanation for UU resistance to cipro- and ofloxacin might be offered by the overuse of these antibiotics for the treatment of various infections (mainly urinary and respiratory tract infections), due to their reduced price and low percentage of side reactions. Studies performed using other diagnostic means have shown that moxifloxacin appears as one of the most active antimicrobial agent against *U. urealyticum* including tetracycline-resistant strains, being nowadays in some countries the drug of choice for the treatment of *Mycoplasma* non-gonococcal nonchlamydial urethritis. Eventually, in the near future, the manufacturer of the Mycoplasma IST2 kit would consider changing ciprofloxacin with moxifloxacin (or adding the latter) in the design of the Mycoplasma IST2 kit.

Some mycoplasmas may develop resistance via gene mutation, acquisition of a resistance gene, or while being protected by biofilms (Garcia-Castillo *et al*., 2008). Multidrug-resistant mycoplasma strains have recently been identified, Chinese researchers having studied strains resistant to up to 14 antibiotics belonging to several classes (Wang *et al*., 2016). In our study only few of the isolated strains were found resistant to a maximum of three classes of antibiotics (macrolides, quinolones and tetracyclines). Nevertheless, the emergence of extensively drug-resistant strains points towards the increasing importance of appropriate antibiotic susceptibility testing both in scientific research and in the clinical settings, as already stated two decades ago (Dosa *et al*., 1999).

Conclusions

Differences between studies performed in closely situated geographical settings confirm that the continuously changing antibiotic resistance of these germs should be followed at least in a few centers in every country, so as to determine the best local therapy options for patients with non-gonococcal sexually transmitted infections.

The prevalence of colonization / infection with genital mycoplasmas in our study and the rising trend of resistance to several classes of antibiotics might become problematic over the next decades. Therefore, antibiotic susceptibility of the strains should be assessed prior to treatment initiation.

Although in Romania doxycycline is the most commonly used antibiotic in the treatment of non-gonococcal genital infections, it continues to be, in the population studied, the most effective agent against mycoplasmas. Our results indicate that tetracycline as well might be an option of choice when empirical therapy is required. Out of the list of antibiotics tested for effectiveness against mycoplasmas by the Mycoplasma IST2 kit, pristinamycin remains an excellent option for selected cases of infection with resistant strains, but unfortunately it is not yet available in Romanian pharmacies, this providing, perhaps, an explanation for the fact that all the mycoplasmas isolated so far by us have been susceptible to this antibiotic.

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