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Occurrence of *Ureaplasma urealyticumin* in Women in the Northeast of Iran: Characterization of Resistance Trends

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Abstract

Objectives: The present study surveyed the prevalence of antibiotic resistance among *Ureaplasma urealyticum* in isolates from Gonabad (in the northeast of Iran) including susceptibility testing for *U. urealyticum* to different antibiotics.

Materials and Methods: In this research, a total of 95 vaginal swab specimens were aseptically collected from women who were admitted to the Bohlool Teaching Hospital and Jahad Daneshgahi Center from April 2016 to April 2017. Culture and subsequently antibiotic susceptibility testing were performed according to the *Mycoplasma* IST 2 kit. Then the cupules were read and interpreted in 24 and 48 hours according to kit guidelines.

Results: In the studied patients, 38 (40.4 %), 12 (12.8 %), and 11 (11.7%) cases were single positive for *U. urealyticum*, single positive for *Mycoplasma hominis (M. hominis)*, and dually positive for *U. urealyticum* and *M. hominis*, respectively. The positive rates of genital *U. urealyticum* in the symptomatic and asymptomatic groups were 86.8% and 13.2%, respectively. The highest positive rate (42.1%) was found in the 26-30-year-old group. In addition, tetracycline (TET) and doxycycline (DOT) were the most effective antibiotics against isolates, and one strain was multi-drug resistant. The *U. urealyticum* resistance rates were more than 39% to erythromycin and pristinamycin, and more than 55% to ciprofloxacin. All *U. urealyticum* isolates with <104 CFU/specimen were sensitive to all tested drugs.

Conclusions: Although the emerging resistance to TETs among our isolates is alarming, these data show that the standard therapeutic regimen for urogenital infections caused by *U. urealyticum* is DOT, TET, and clarithromycin, leading to better outcomes in most respective patients.

Keywords: Women, Urogenital infection, *Ureaplasma urealyticum*, Antibiotic susceptibility pattern

Introduction

Ureaplasma urealyticum is the smallest and simplest self-replicating bacterium belonging to the class Mollicutes and is only bounded by the bacterial membrane (1). This organism is highly fastidious and completely dependent on host biosynthetic precursors (2). It is frequently isolated from human amniotic fluid and the placenta. Approximately 40-80% of healthy adult women may be the carrier of *Ureaplasmas* in their cervix and vagina. The occurrence of *Ureaplasma* in the healthy men's lower urogenital tract is somewhat less (3).

Ureaplasma urealyticum is easily transmitted vertically and venereally either at the delivery of the neonate or *in utero* (2). It is in the neonatal respiratory tract or a colonizer of the female and male urogenital systems. The pathogenicity of this bacterium in urethritis has been documented in some studies (4,5). *Ureaplasma* species may cause or be related to a variety of clinical manifestations in adults, including meningitis, preterm birth, postpartum endometritis, urethritis, chorioamnionitis, chronic lung disease in neonates, abscesses, arthritis, bacteremia, and pneumonia (2,6).

The systemic spread of this bacterium is possible in the immunosuppressed condition beyond the neonatal period, including hypogammaglobulinemia (2). *U. urealyticum* causes nongonococcal urethritis in humans and has also been associated with chorioamnionitis, abortion, infertility, low-weight infants, premature rupture of membranes, preterm labor, and preterm delivery and leads to apparently normal pregnancy outcomes (7).

After the diagnosis of *Ureaplasma* infection, selective drugs are confined for treatment. The absence of the

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Key Messages

- The tetracycline and erythromycin resistant strains emerging in our investigation are really *alarming*. The important risk for drug resistance emerging in *Ureaplasma uralyticum* has potential clinical sequels in therapeutic guidelines.

cell wall renders *U. urealyticum* intrinsically resistant to all effective drugs on the bacterial cell wall such as glycopeptide and β-lactam antibiotics (8). According to García-Castillo et al study (9), antibiotic classes which are recognized to be effective against *Ureaplasma* include macrolides, quinolones, and tetracyclines (TETs). These therapy choices are further limited in the neonates for whom the only recognized treatment is to use macrolides because of the related toxicity of TETs and quinolones (10).

Considering the above-mentioned explanations, the main goal of the present research was to find the role of *U. urealyticum* in clinical problems occurring in the genitourinary tract of women by the culturing method and to determine the antibiotic susceptibility patterns of the isolates. The study further investigated the prevalence of resistance to antibiotics among *U. urealyticum* strains isolated from Gonabad (Khorasan Razavi province, in the northeast of Iran). Finally, *in vitro* susceptibility testing was performed for *U. urealyticum* to different antibiotics.

Materials and Methods

Clinical Specimen Collection

The present study was carried out after approval of the Ethics Committee of Gonabad University of Medical Sciences (The code number IR.GMU.REC.1393. 12727.4.5). In total, 95 vaginal swab samples were aseptically obtained from women admitted to the Bohlool Teaching Hospital and Jahad Daneshgahi Center, in Gonabad from April 2016 to April 2017. The specimens were collected from married and unmarried women either pregnant or non-pregnant and included vaginal Dacron swabs containing two samples from each woman. The *Mycoplasma* R1 vial was allowed to reach laboratory temperature. Afterward, Dacron swabs were directly placed in the *Mycoplasma* R1 solution (a special transport medium) to maintain the swab wet. The inoculated vial of *Mycoplasma* R1, coated in an ice bag and protected from the light, was transported to the clinical microbiology laboratory for culture and subsequently antibiotic susceptibility testing. The transport medium vial was mixed, and subsequently,3 milliliters of the inoculated *Mycoplasma* R1 solution vial was transferred into the *Mycoplasma* R2 vial shaken on a vortex to ensure that the lyophilization pellet was quite dissolved. This inoculum was applied to inoculate the *Mycoplasma* IST 2 strip, and then it was allowed to reach laboratory temperature. The diagnostic strip was removed from its packaging. Immediately, 55 µL of the broth medium was dispensed into each of the 22 test cupules on the *Mycoplasma* IST 2 strip by the pipette. Next, 2 drops of the mineral oil were added to each cupule and the lid was placed on the strip. The remaining strip and the broth in the Mycoplasma R2 vial were incubated at 36°C±2 for 24 and 48 hours. The change in the color of the Urea-Arginine LYO 2 broth was read after 24 and 48 hours of incubation. Finally, the cupules were read and interpreted in 24 and 48 hours except for *Ureaplasma* spp. ≥10^4 CFU/specimen which was read in 24 hours.

Determination Antibiotic Susceptibility Patterns of *Ureaplasma urealyticum*

The *Mycoplasma* IST 2 diagnostic kit was applied for the characterization of antibiotic susceptibility patterns. The broth medium prepares optimum replication and growth conditions for *U. urealyticum*. This strip (cupules) provides simultaneous results for the susceptibility testing of isolates with 9 different antibiotics. These antibiotics included doxycycline (DOT, concentrations of 4 and 8 mg/L), josamycin (JOS, concentrations of 2 and 8 mg/L), ofloxacin (OFL, concentrations of 1 and 4 mg/L), erythromycin (ERY, concentrations of 1 and 4 mg/L), TET (concentrations of 2 and 8 mg/L), ciprofloxacin (CIP, concentrations of 1 and 2 mg/L), azithromycin (AZI, concentrations of 0.12 and 4 mg/L), clarithromycin (CLA, concentrations of 1 and 4 mg/L), and pristinamycin (PRI, 2 mg/L).

Multi-drug Resistant *U. urealyticum* Isolate Detection

Multi-drug-resistant *U. urealyticum* isolates were defined to be resistant to at least three antibiotics indifferent classes of antimicrobial drugs (including ERY, CIP, and TET) by the Kirby-Bauer disk diffusion technique. The results were analyzed in accordance with the Clinical and Laboratory Standards Institute (CLSI) (2015) guidelines.

Statistical Analysis

The results were analyzed by SPSS 16 statistical software. *P* values ≤0.05 were considered statistically significant. Standard deviations and means were calculated as required for numerical variables.

Results

In general, 95 vaginal swab specimens submitted to the clinical microbiology laboratory in the Mycoplasma R1 solution for *U. urealyticum* culture were evaluated in the present study. The titer was low in 11 (11.5%) samples, thus the color change was observed in the Mycoplasma R1 transport medium vial only and not in the control cupule on the strip (the titer of the bacteria in the sample is too low to produce the color change). The analysis of culture results revealed that the prevalence rate of *U. urealyticum* infection was 40.4% (95% CI 39.45%-41.35%). Based on the results, 11 out of 38 *U. urealyticum* infected women

had a co-infection with *Mycoplasma hominis*. Table 1 presents the key characteristics of the study population regarding sexual behavior and sociodemographic status.

In these studied patients, 12 (12.8 %) and 38 (40.4 %) cases were single positive for *M. hominis* and *U. urealyticum*, respectively, and 11 (11.7%) cases were dually positive for *M. hominis* and *U. urealyticum* (Table 1). The bacteria concentration in 33 (35.1%) isolates was higher than 10^4 while it was lower than 10^4 in 5 (5.3%) isolates. There was no significant relation between *U. urealyticum* counts and menstrual cycles.

However, a significant relationship was found between *U. urealyticum* infected patients and their husbands' educational level ($P=0.04$). Respectively, the positive rates of genital *U. urealyticum* in the asymptomatic and symptomatic groups were 13.2% and 86.8%, respectively. In the univariate analysis of socio-demographical associated with *U. urealyticum* in the studied women, the increasing weight of patients was especially associated with a greater risk of being infected. The total positive rates of genital *U. urealyticum* in 26-35-year-old individuals were relatively higher compared with the other age groups and drastically reduced in womenover46 years. The highest positive rate (42.1%) was found in the 26-35 year age group. However, the positive rates in women living with their husbands and those living in separation revealed a significant difference ($P = 0.05$).

Tables 2 and 3 provide data on the antibiotic susceptibility patterns of *U. urealyticum* isolates. TET and DOT were the most effective drugs against those strains. For *U. urealyticum*, the obtained rates of susceptibility to some antibiotics by the IST 2 diagnostic kit included DOT (92.1%), TET (92.1%), azithromycin (AZT, 65.8%), OFL (65.8%), ERY (60.5%), and PRI (60.5%). In the analysis of the isolates, one strain was multi-drug-resistant. The resistance rates of *U. urealyticum* were more than 39%to ERY and PRI, and more than 55% to CIP while the rates were lower than 8% to DOT and TET (Table 2). Based on the results, 28.9% of the strains revealed decreased response (intermediate susceptible) to the more newly presented quinolones (OFL). None of the isolates was intermediate susceptible to DOT. Among the studied isolates, the higher intermediate response to drugs was shown for CIP (36.8%, n=14). Among the macrolide class of antibiotics, CLA was the most effective one against the isolates. All *U. urealyticum* isolates with $<10^4$ CFU/specimen were susceptible to all tested antibiotics.

Table 1. Demographic Analysis of *Ureaplasma urealyticum* Positive Patients (n = 38)

Variable	No. (%)
Age (y)	
15-25	10 (26.3)
26-35	16 (42.1)
36-45	10 (26.3)
≥46	2 (5.3)
Weight (kg)	
31-40	1 (2.6)
41-50	3 (7.9)
51-60	8 (21.1)
≥61	26 (68.4)
Job	
Housewife	31 (81.6)
Jobholder	7 (18.4)
Education level	
Cycles	12 (31.6)
Diploma	16 (42.1)
Collegiate	10 (26.3)
Infertility	
Yes	0 (0)
No	38 (100)
Urinary tract infection	
Yes	12 (31.6)
No	26 (68.4)
Genital infection	
Yes	15 (39.5)
No	23 (60.5)
Drug use	
Yes	6 (15.8)
No	32 (84.2)
Genital infection symptom	
Pruritus	2 (5.3)
Irritation	1 (2.6)
Genital secretion	7 (18.4)
Pelvic pain	1 (2.6)
Asymptomatic	5 (13.2)
Some of these signs	22 (57.9)
Husband education	
Cycles	14 (36.8)
Diploma	11 (29)
College	13 (34.2)
Contraception	
Drug	3 (7.9)
Condom	14 (36.8)
Natural	13 (34.2)
Tubectomy	2 (5.3)
IUD	1 (2.6)
Ampulla	1 (2.6)
Marriage age	
1-10 y	22 (57.9)
11-20 y	11 (28.9)
21-30 y	5 (13.2)
Child number	
0-2	31 (81.6)
3-5	7 (18.4)
Antibiotic usage	
Yes	9 (23.7)
No	29 (76.3)
Hospitalization	
Yes	7 (18.4)
No	31 (81.6)
Medical device	
Yes	2 (5.3)
No	36 (94.7)
Preterm delivery	
Yes	1 (2.6)
No	37 (97.4)

Discussion

The current study sought to determine the prevalence, antimicrobial susceptibility patterns, resistance profiles, and the multidrug resistance of *U. urealyticum* recovered from patient samples in Gonabad in the north-eastern of Iran.

In the past decade, *U. urealyticum* received further attention because of its association with preterm

Table 2. The *Ureaplasma urealyticum* Antimicrobial Susceptibility Profile (n = 38)

	DOT	TET	OFL	CIP	JOS	ERY	CLA	AZT	PRI
Susceptible	35 (92.1)	35 (92.1)	25 (65.8)	17 (44.7)	22 (57.9)	23 (60.5)	27 (71.1)	25 (65.8)	23 (60.5)
Intermediate	0 (0)	1 (2.6)	11 (28.9)	14 (36.8)	11 (28.9)	7 (18.4)	4 (10.5)	6 (15.8)	-
Resistant	3 (7.9)	2 (5.3)	2 (5.3)	7 (18.4)	5 (13.2)	8 (21.1)	7 (18.4)	7 (18.4)	15 (39.5)
Total	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)	38 (100)

Note. DOT: Doxycycline; TET: Tetracycline; OFL: Ofloxacin; CIP: Ciprofloxacin; JOS: Josamycin; ERY: Erythromycin; CLA: Clarithromycin; AZT: Azithromycin; PRI: Pristinamycin.

Table 3. Antimicrobial Resistance Pattern of Ureaplasma urealyticum Isolates With ≥10^4 CFU and <10^4 CFU

	ERY	CLA	AZT	CIP	OFL	DOT	TET	JOS	PRI
≥104 CFU/specimen (n=33)	45.4%	33.3%	39.4%	63.6%	39.4%	9.1%	9.1%	48.5%	45.4%
<104 CFU/specimen (n=5)	100%	100%	100%	100%	100%	100%	100%	100%	100%

Note. ERY: Erythromycin; CLA: Clarithromycin; AZT: Azithromycin; OFL; Ofloxacin; CIP: Ciprofloxacin; DOT: Doxycycline; TET: Tetracycline; JOS: Josamycin; PRI: Pristinamycin.

birth, postpartum infections, urogenital diseases, and adverse pregnancy outcomes (11). Given the frequent implementation of diagnostic techniques that only recognize causative organisms, these bacterial infections are generally treated by TETs, macrolides (i.e., AZI, ERY, and clarithromycin), or fluoroquinolonesin empirical therapy (12). Nevertheless, information regarding the antimicrobial sensitivity profile of genital mycoplasmas is limited, and regional statistics are exclusively required to establish efficient treatments.

Considering antibiotic susceptibility outcomes, the results of the present research showed that *U. urealyticum* isolates exhibited a high rate of resistance to fluoroquinolones (55.2% of the isolates were resistant or intermediate-susceptible to CIP), which is consistent with the results of another research. Overall, the highest antibiotic resistance rates have been reported against fluoroquinolones in most geographical regions (12,13). Two Chinese analyses reported fluoroquinolone resistance rates of 40% for *Ureaplasma* spp. (12). The resistance is mostly because of antibiotics overuse in different industries and human communities (e.g., for different infections including urinary and respiratory systems diseases), which contributes to the selection of drug-resistant *U. urealyticum* (14,15). Given that many CIP-resistant isolates are susceptible to TETs (i.e., TET and DOT), treatment should involve monotherapy or combination therapy including TETs.

In this investigation, 42.1% of the surveyed strains were non-susceptible to JOS, but the prevalence of resistance to PRI was lower (39.5%). Further, the rate of JOS resistance was much higher compared to a study on the rate of JOS resistant *U. urealyticum* (58.7%) in Bern, Switzerland (12). The same increase in the rate of JOS resistance *U. urealyticum* has been reported earlier in different studies reported from several regions of the world (16). In the present study, 39.4% of 33 *U. urealyticum* isolates with ≥10^4 CFU were resistant to OFL while all isolates with <10^4 CFU were susceptible to all tested antibiotics.

As revealed, 9.1% of the strains were insensitive to DOT and TET. These results are in line with prior studies from Switzerland and China which reported that all strains were sensitive to these antibiotics (12,17). Therefore, TET resistant strains emerging in our investigation are really alarming. The important risk for drug resistance emerging in *U. urealyticum* has potential clinical sequels in therapeutic guidelines. In other fields such as plants, poultries, food animals, fish, and other sources, antimicrobial agents are applied for various purposes potentially leading to emerging insensitive isolates.

Furthermore, a high rate of ERY-resistant *U. urealyticum* (i.e., 39.5%) was observed in contrast with the rates from Romania, which was reported 16.09%. Resistance to AZI and CLA has been reported at 8.05%, and 9.19%, respectively in Romania as well (18).

Pristinamycin resistant isolates (39.5%) detected in our study are quite alarming. Our data contradict those of other studies from different geographical regions, presenting the high sensitivity to this drug among *U. urealyticum* isolates (12,19,20).

In Chinese studies, the prevalence rates of TET and macrolide non-susceptible strains were 10% and 30%, respectively (21,22). In Croatia, *U. urealyticum* strains showed resistance rates of 3%, 8%, and 22% for DOT, AZI, and OFL, respectively (13). In South Africa, the non-susceptibility rates of ERY, moxifloxacin, TET, and levofloxacin were 80%, 2%, 73%, and 41%, respectively (23). These contradictions in resistance rates among the aforementioned reports could be due to the usage of different techniques and criteria for the interpretation of susceptibility results.

Although the emerging resistance to TETs among our isolates is alarming, the reports by the Schneider et al indicated that the therapeutic protocols for urogenital infections caused by *U. urealyticum* include DOT, TET, and clarithromycin (12), leading to efficient outcomes in

most respective patients.

Research on other pathogenic bacteria such as foodborne pathogens in women is necessary. Hormonal changes that occur in pregnancy reduce cell-dependent immunity, thus raising the susceptibility of pregnant women to some microbial infections. Foodborne diseases may be worrying in pregnancy and can lead to preterm delivery or abortion and serious sequelae in newborn babies (24-29).

Conclusions

Culture is still the most widely used means for the isolation and identification of genital *Ureaplasma* spp. in human samples, and it remains the accepted reference standard. These bacteria are highly sensitive to unfavorable conditions (i.e., heat and drying) in the environment, thus great attention must be paid to ensure proper specimen collection and transport. Dacron, polyester, or calcium alginate swabs with plastic shafts or aluminum are more suitable. To collect swabs, we should select the sites where most cells can be obtained because *Ureaplasma* spp. are cell-associated.

Authors' Contribution

All authors contributed to this study equally.

Conflict of Interests

Authors declare that they have no conflict of interests.

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