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ANALYSIS OF CANDIDA SPECIES DISTRIBUTION ISOLATED FROM WOMEN WITH VULVOVAGINAL CANDIDIASIS AND THEIR ANTIFUNGAL SUSCEPTIBILITY PROFILE

Abstract. Background. *Candida* species is usually a commensal fungus residing in the vagina, in about 30 %–50 % of healthy adults and remains the most common agent isolated from clinical samples of patients diagnosed with vulvovaginal candidiasis (VVC). Culture is not recommended for all patients on a routine basis but is informative for the exclusion of non-albicans infections resistant to azoles, or recurrent VVC. Identification of *Candida* species and antifungal susceptibility testing are key elements in the correct management of recurrent VVC. The authors of this paper aimed to study the spectrum of pathogenic *Candida* species. The antifungal sensitivity patterns of the isolated strains during the years 2017-2019 are also presented. **Material and methods.** A descriptive study of *Candida* species distribution and antifungal susceptibility profile was performed. Identification of isolated *Candida* species was performed by the MALDI-TOF MS, bacterial strains by Vitek 2 automated system (BioMérieux) and antifungal susceptibility profiles by Fungitest (Bio-Rad). **Results.** Of the 1030 recovered strains, *C. albicans* species predominated - 83.8% and *Candida non albicans* -16.2%. The most common species of the *Candida non-albicans*, were *C. glabrata* (7.5%). Also, it was observed that in 56.6% of the cases *C. albicans* presented bacterial associations. The most common microbial association was *C. albicans* and *S. aureus* (26.6%), followed by *C. albicans* and *E. coli* (20.8%). *Candida* spp. showed moderate antifungal resistance. The resistance rate of *C. albicans* isolates to miconazole, fluconazole and itraconazole was 25.5%, 17.0% and 11.4% compared to non-albicans *Candida* strains which showed a resistance rate of 10.8%, 14.4% and 10%, respectively. **Conclusions.** *C. albicans* is the most frequently isolated species among patients with VVC, but there is also an increase share of non-albicans *Candida* species such as *C. glabrata*. *C. albicans* isolates showed higher indices of resistance, than *Candida non-albicans*.

Keywords: *Candida non-albicans*; *Candida albicans*; VVC; antifungal agents

Introduction

Candida species, which are part of the normal flora in the vagina in small quantities but in some cases may be involved in human pathology and at least 20 % of women, cause opportunistic infections. This situation happens in some circumstances that compromise host immunity (hormone replacement, uncontrolled diabetes mellitus, long-term broad-spectrum antibiotic treatment, surgical manipulation of the vagina, and immunosuppression) [1].

According to recent studies the disturbance of local host defense mechanisms limiting *Candida* growth also lead to vulvovaginal candidiasis (VVC) [1, 2].

VVC is a common problem worldwide and is multifactorial in origin, affecting millions of women annually, with serious impact on their quality of life and is associated with significant direct and indirect costs [3, 4].

Currently, there are official reports, studies that have shown that in Europe VVC is one of the most common causes of vaginitis, and in the United States, it is the se-

cond most frequent cause of infection after bacterial vaginosis [5, 6].

The complex research conducted by a group of authors has been estimated that 75 % of all women will experience at least one episode of VVC in their lives. Between 40 % and 50 % of initially infected women will experience a second episode [5, 6].

The study focused on the analysis of the articles that approached mainly factors predisposing to VVC highlighted the following factors: contraceptives usage, and also poor personal hygiene and some sexual and clothing habits [5].

Literature described VVC reports on studies based on women's questionnaires on their self-reported history of vulvovaginal candidiasis, but without laboratory diagnoses that confirm infection with *Candida* [7].

Other studies show that frequently the women practice self-diagnosis and treatment across the counter, while others merely endure the infection which leads to the development of antifungal resistance thus the problem of antifungal resistance [8, 9].

According to research data, the clinical diagnosis of vaginal candidiasis is unreliable, and laboratory confirmation is needed which will identify the etiological agents and their susceptibility to antifungals for providing effective therapy [7, 9].

The scientific research published during the last two decades presents evidence that, the most common *Candida* species associated with VVC are *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*. The authors highlighted that commonly a single species, but two or more species have been found in some women with VVC (1–10 %) [10].

Also, other studies demonstrated that in more than 70 % of cases, VVC is caused by *C. albicans*, followed by *C. glabrata*, *C. tropicalis*, *C. parapsilosis* and *C. krusei* [11, 12].

In recent times, however, there has been a notable shift in the etiology of candidiasis with non-*albicans Candida* (NAC) species gaining prominence. An increasing trend of VVC caused by non-*albicans Candida* species (NAC) has been reported due to the widespread use of antifungal agents that are frequently available over-the-counter [13, 14].

Since none of the clinical signs of vulvovaginal candidiasis is pathognomonic, clinical the diagnosis must always be confirmed by laboratory methods [15].

There is evidence from few studies which emphasizes the importance of laboratory diagnosis in management of VVC and which have diagnosed the vulvovaginal candidiasis through laboratory confirmation of infection in symptomatic women [16].

Currently, some studies and guidelines recommend laboratory culture of the vulvovaginal specimen for the effective management of VVC, accordingly clinical evaluation and laboratory culture should be the standard diagnostic method [17].

Culture is not recommended for all patients on a routine basis, as colonization can be detected rather than infection. This diagnostic method is informative for the exclusion of non-*albicans* infections resistant to azoles, or in the case of a recurrent VVC [18, 19, 20].

The purpose of this study was undertaken to evaluate the *Candida* species distribution isolated from vaginal swab and their antifungal susceptibility patterns.

Materials and methods

During the 2017–2019, after microbiological analyzes 1030 isolates were recovered from the clinical samples. Specimens were taken from the posterior fornix of the vagina with sterile swabs and transported to the microbiology laboratory for further processing.

Culture isolation and identification

For the isolation of *Candida* spp., specimens were inoculated on *Sabouraud* dextrose agar supplemented with chloramphenicol (Oxoid) and incubated at 36°C for 72 hours. Simultaneously, with the fungal strains, other associated bacterial strains were isolated. Identification to the species level was performed by MALDI-TOF MS (Bruker Daltonics) and bacterial strains by Vitek 2 automated system (BioMérieux).

Antifungal susceptibility testing

The in vitro activity of the antifungal agents against each isolate was determined by using Fungitest galleries (Bio-Rad SDP Paris, France).

Inoculum preparation

From the isolated colonies an inoculum was prepared by suspending them in 3 ml of sterile saline (aqueous solution of 0.50 % NaCl, pH - 7.0). To obtain a turbidity equivalent to that of the McFarland 0.50 standard, the measurements were performed with the PhoenixSpec nephelometer (Becton Dickinson). Subsequently, the antifungal susceptibility test was performed by inoculating the Fungitest microplates and incubating at 37° C for 24–48 hours.

Interpretation of results

The results were interpreted based on interpretive susceptibility criteria for antifungal breakpoints from EUCAST (European Committee on Antimicrobial Susceptibility). Isolates with minimum inhibitory concentration (MIC): <2µg/ml for amphotericin B, <2 µg/ml - 5 flucytosine, <0.5 µg/ml -miconazole, <0.5 µg/ml -ketoconazole, <0.5 µg/ml -itraconazole, <8 µg/ml -fluconazole) were considered susceptible.

Quality control of the investigation. For quality control, *C. albicans* (ATCC 10231) was used as reference strain and tested simultaneously with the clinical isolates.

Results and discussions

After microbiological analyzes 1030 isolates were recovered from the clinical samples. Information regarding the prevalence of VVC in Moldova is not well known and varies from one study to another. Literature evidence regarding VVC reports highlighted that this disease it is the second most common infection of the vulvovaginal area of symptomatic women accounting for about 17 % to 42 % [21, 22, 23].

Regrettably, this disease is routinely diagnosed by sign and symptom and is not confirmed with laboratory investigation when necessary. As a result, the spectrum of yeasts implicated in causing the disease, their drug susceptibility profile is not known in the country.

Studies demonstrate the necessity of identification the *Candida* species responsible for infections in all patients presenting with VVC especially those with recurrent infections. Therefore, identification will influence selection of antifungals and duration of therapy [23, 24].

Between 85% to 90% of yeast strains isolated from the vagina belong to the *Candida albicans* species; other yeasts account for up to 15 % (8-10) of cases [24, 25, 26].

Assessing the prevalence of the identified subtypes, the predominance of *C. albicans* species was found (n=863; 83.8%), compared to non-*albicans Candida* species (n=167; 16.2%). The most common non-*albicans* species were *C. glabrata* (n=77; 7.5%) followed by *C. robusta* (n=28; 2.7 %), *C. krusei* (n=24; 2.3 %), *C. kefyr* (n=12; 1.2 %), *C. parapsilosis* (n=9; 0. %) and other species (n=17; 1.7 %).

Simultaneously, compared to previous years, a trend has been observed and that is an increase in the rate of isolation of non-*albicans Candida* species. This phenomenon could be due to the improvement of laboratory diagnostic practices regarding the identification of fungi or a real higher prevalence of these species [25, 26].

Of the total number of 1030 *Candida* isolates, 584 (56.6 %) showed bacterial associations.

The most common microbial association was *C. albicans* and *S.aureus* - 127 combinations (26.6 %), followed by *C. albicans* and *E.coli* - 99 combinations (20.8 %). Bacterial associations with non-*albicans Candida* species or recorded less frequently.

The clinical significance of the identification of the *Candida* to the species level is definite and completely recognized by the majority of studies on the reason for the diversity of expression of virulence factors and their susceptibility to antifungal agents. The support of the laboratory is crucial in order to fight vaginal *Candida* infection with targeted therapy [27].

Antifungal susceptibility test results show that most isolates were sensitive to 5-fluorocytosine followed by amphotericin B and ketoconazole. *Candida* species have shown moderate indices of resistance to miconazole, fluconazole and itraconazole.

Isolates of *C. albicans* have been shown to be more resistant to these medications than non-*albicans Candida*. The resistance rate of *C. albicans* isolates to miconazole, fluconazole and itraconazole was 25.5 %, 17.0 % and 11.4 %, compared to non-*albicans Candida* strains with a resistance rate of 10 %, 14.4 % and 10 %.

Finally, the variety of non-*albicans Candida* species involved in human pathology, their rising contribution to fungal infections and the antifungal susceptibility profiles makes their identification at the species level essential for epidemiological investigations, optimizing therapy and patient management.

Conclusions

Candida albicans was the most common isolated fungal species among patients with vulvovaginitis, and there is an increasing tendency of isolation of *Candida* non-*albicans* species, a phenomenon found by other similar research.

Analyzing the clinical isolates in this research, associations of *Candida* spp. with other microorganisms were also observed. *Candida albicans* with *S. aureus* was the most common, followed by *Candida albicans* and *E.coli*.

Based on the antifungal susceptibility test results, it was found that most isolates were susceptible to 5-fluorocytosine and amphotericin B, ketoconazole and moderately resistant to miconazole, fluconazole and itraconazole. *C. albicans* have been shown to be more resistant than non-*albicans Candida*.

Additional studies on a larger sample and evaluating results of antifungal susceptibility testing are of great importance for optimizing therapy and patient management to fighting vaginal *Candida* infections with targeted therapy.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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АНАЛІЗ ПОШИРЕННЯ ВИДІВ CANDIDA, ВИДІЛЕНИХ У ЖІНОК З КАНДИДОЗНИМ ВУЛЬВОВАГІНИТОМ, І ПРОФІЛІ ЇХ ЧУТЛИВОСТІ ДО ПРОТИГРИБКОВИХ ПРЕПАРАТІВ

Резюме. *Актуальність.* Зазвичай види *Candida* – це комменсальна грибок, що живе в піхві, приблизно, 30-50 % здорових дорослих жінок, який є найбільш частим збудником, виділеним з клінічних зразків пацієнток з діагнозом вульвовагінальний кандидоз (ВВК). Культуральний метод не рекомендується для всіх пацієнтів на регулярній основі, але він інформативний для виключення non-albicans інфекцій, стійких до азолів, або рецидивів ВВК. Визначення видів *Candida* і тестування на чутливість до протигрибкових препаратів є ключовими елементами в правильному веденні рецидивуючого ВВК. Автори даної статті ставили перед собою мету вивчити спектр патогенних видів *Candida*. Також представлена картина протигрибкової чутливості виділених штамів за 2017-2019 роки. **Матеріалу**

та методи. Проведено описову дослідження поширення видів *Candida* і їх чутливості до протигрибкових препаратів. Ідентифікацію ізольованих видів *Candida* проводили за допомогою MALDI-TOF мас-спектрометрії, штамів – за допомогою автоматизованої системи Vitek 2 (BioMérieux), а профілі протигрибкової чутливості – за допомогою Fungitest (Bio-Rad). **Результати.** З 1030 оброблених штамів переважали види *C. albicans* – 83,8 %, *Candida non-albicans* – 16,2 %. Найбільш поширеним видом *Candida non-albicans* була *C.glabrata* (7,5 %). Також було відмічено, що в 56,6 % випадків *C. albicans* представляла частина бактеріальної асоціації. Найбільш частими мікробними асоціаціями були *C. albicans* і *S.aureus* (26,6 %), потім слідували *C. albicans* і *E.coli* (20,8 %). Види *Candida* по-

казали помірну стійкість до протигрибкових препаратів. Рівень стійкості ізолятів *C. albicans* до міконазолу, флуконазолу та ітраконазолу становив 25,5 %, 17,0 % і 11,4 % відповідно, у порівнянні зі штамми *Candida non-albicans*, які показали рівень стійкості 10,8 %, 14,4 % і 10 %, відповідно. **Висновки.** *C. albicans* є найбільш часто ізольованим видом серед пацієн-

ток з ВВК, але також спостерігається підвищена частка видів *Candida non-albicans*, таких як *C. glabrata*. Ізоляти *C. albicans* показали більш високі показники лікарської стійкості, ніж *Candida non-albicans*.

Ключові слова: *Candida non-albicans*; *Candida albicans*; ВВК; протигрибкові препарати

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АНАЛИЗ РАСПРОСТРАНЕНИЯ ВИДОВ *CANDIDA*, ВЫДЕЛЕННЫХ У ЖЕНЩИН С КАНДИДОЗНЫМ ВУЛЬВОВАГИНИТОМ, И ПРОФИЛИ ИХ ЧУВСТВИТЕЛЬНОСТИ К ПРОТИВОГРИБКОВЫМ ПРЕПАРАТАМ

Резюме. Актуальность. Обычно виды *Candida* - это комменсальный грибок, обитающий во влагалище примерно 30–50% здоровых взрослых женщин, который является наиболее частым возбудителем, выделенным из клинических образцов пациенток с диагнозом вульвовагинальный кандидоз (ВВК). Культуральный метод не рекомендуется для всех пациентов на регулярной основе, но он информативен для исключения *non-albicans* инфекций, устойчивых к азолам, или рецидивов ВВК. Определение видов *Candida* и тестирование на чувствительность к противогрибковым препаратам являются ключевыми элементами в правильном ведении рецидивирующего ВВК. Авторы данной статьи ставили перед собой цель изучить спектр патогенных видов *Candida*. Также представлена картина противогрибковой чувствительности выделенных штаммов за 2017-2019 годы. **Материалы и методы.** Проведено описательное исследование распространения видов *Candida* и их чувствительности к противогрибковым препаратам. Идентификацию изолированных видов *Candida* проводили с помощью MALDI-TOF масс-спектрометрии, штаммов – с помощью автоматизированной системы Vitek 2 (BioMérieux), а профили противогрибковой чувствитель-

ности - с помощью Fungitest (Bio-Rad). **Результаты.** Из 1030 обработанных штаммов преобладали виды *C. albicans* – 83,8 %, *Candida non-albicans* – 16,2 %. Наиболее распространенным видом *Candida non-albicans* была *C. glabrata* (7,5 %). Также было замечено, что в 56,6 % случаев *C. albicans* представляла часть бактериальной ассоциации. Наиболее частыми микробными ассоциациями были *C. albicans* и *S.aureus* (26,6 %), затем следовали *C. albicans* и *E.coli* (20,8 %). Виды *Candida* показали умеренную устойчивость к противогрибковым препаратам. Уровень устойчивости изолятов *C. albicans* к миконазолу, флуконазолу и итраконазолу составлял 25,5 %, 17,0 % и 11,4 % соответственно, по сравнению со штаммами *Candida non-albicans*, которые показали уровень устойчивости 10,8 %, 14,4 % и 10 % соответственно. **Выводы.** *C. albicans* является наиболее часто изолированным видом среди пациенток с ВВК, но также наблюдается повышенная доля видов *Candida non-albicans*, таких как *C. glabrata*. Изоляты *C. albicans* показали более высокие показатели лекарственной устойчивости, чем *Candida non-albicans*.

Ключевые слова: *Candida non-albicans*, *Candida albicans*, ВВК, противогрибковые препараты.