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RESEARCH ANTIFUNGAL THERAPY OF OROPHARYNGEAL CANDIDIASIS IN HIV-INFECTED PATIENTS

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Modern medicine has made significant advances in the treatment of fungal infections. The problem of drug resistance of such a common conditional pathogen as Candida remains relevant for the last decade. The aims of the study were: 1) analysis of species and strain drift of Candida in patients with HIV/AIDS from oropharynx and intestine in two years; 2) the analysis of the dynamics of the sensitivity of Candida to standard antimycotic drugs. Treatment of candidiasis in HIV-infected patients leads to changes in the species and strain composition of Candida. After eradication of C. albicans which is sensitive to fluconazole, more resistant strains of other species (glabratae, krusei. tropicalis) takes its place in the biotope, which is one of the reasons for the low effectiveness of antimycotic therapy.

K e y w o r d s : *candidiasis, HIV, antimycotic resistance.*

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АНТИМИКОТИЧЕСКАЯ ТЕРАПИЯ ОРОФАРИНГЕАЛЬНОГО КАНДИДОЗА У ВИЧ-ИНФИЦИРОВАННЫХ ПАЦИЕНТОВ

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Представители рода Candida - это возбудители оппортунистической инфекции, многократно усиливающие свой патогенный потенциал в условиях нарушений в иммунной системе хозяина, вследствие чего может не только ухудшаться прогноз основного заболевания у ВИЧ-инфицированных пациентов, но может стать причиной летального исхода.

Вместе с тем, нарастающая антимикотикорезистентность Candida spp. у ВИЧ-инфицированных пациентов, нередко получающих длительное время антифунгальные препараты, как с профилактической, так и с лечебной целью обуславливают необходимость разработки эффективных схем лечения на основе изучения устойчивости Candida spp. к противогрибковым препаратам на видовом и генетическом уровнях.

К л ю ч е в ы е с л о в а : *кандидоз, Candida, резистентность, антимикотическая терапия, ВИЧ-инфекция.*

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Background

The most common candidiasis in HIV-infected individuals is *C. albicans* (up to 62%) [3]. Among the other species (non-albicans Candida) *C. glabrata* (46,4%), *C. parapsilosis* (24.7 %), *C. tropicalis* (13.9 %) were recognized as dominant.

The vast majority of OPC and CE are caused by *Candida albicans*, however, lately there has been a tendency of increased cases of non-albicans candidiasis, more difficult to treat [11, 12-15] .

Aims. Analysis of species / strain drift of *Candida* fungi in HIV-infected patients with oropharyngeal candidiasis in 2015 and 2017. Assessment of the sensitivity dynamics of *Candida* genes isolated from HIV-infected fungi to standard antimycotic drugs.

Materials and methods

The study of *Candida spp*. samples obtained from the oropharynx of HIV-infected patients with OFC in

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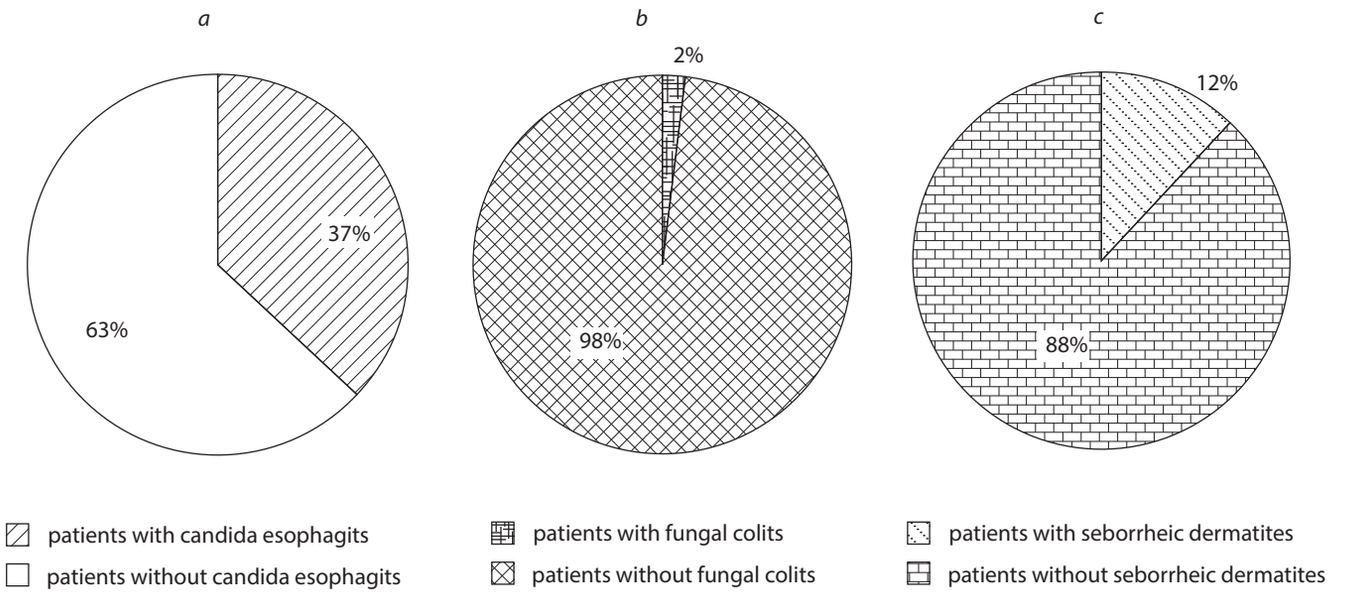

Figures 1, *a, b, c.* distribution of HIV-infected patients according to the presence of candida esophagitis (Fig. 1, *a*), fungal colitis (Fig. 1, *b*), and seborrheic dermatitis (Fig. 1, *c*).

2015 and 2017 was conducted on the basis of the State Budgetary Healthcare Institution Infectious Clinical Hospital № 2 Moscow's Healthcare Department ethical department. In 2015 the study included 19 patients, in 2017- 30 patients of whom 51% were men and 49% - women. Patients aged from 20 to 69 years (median of 38 years), 55% were patients aged 30-40, both women and men. The period of observation of patients by the time of examination was on average 6 years. Standard and additional methods of examination of HIV-infected patients were used, according to the order of the Ministry of Healthcare of the Russian Federation № 474 of 09/07/07.

A publication ethics is composed based on the international standards of the Committee on Publication Ethics. Diagnosis of opportunistic infections by polymerase chain reaction (PCR) were based on sputum investigation (m2000 04J72-01 Abbott Molecular). To highlight the cultures of *Candida spp.* samples of feces and smears from the oropharynx obtained from HIV-infected patients were deposited on the blood agar with a tampon; the materials were incubated in a thermostat for 24 hours at a temperature of 37 ºC.

The obtained isolates were cultivated on CHROMagar, after which the approximate differentiation of fungi by colonies color was made. The sensitivity assessment to antimycotics was carried out by the disco-diffusion method (Oxoid, Great Britain). Biochemical studies were also carried out using commercial test systems (Remel, Erba Lachema, Czech Republic). As a control method of species identification, a multiplex PCR with species-specific primers (Amplisens, Czech Republic) was used.

Diagnosis of opportunistic infections by PCR method was performed on the basis of sputum studies, including HES CMV, HSV type 6, HPG1, type 2, MWT, *Candida albicans, C. glabrata, C. krusei, C. parapsilosis* (m2000 04J72-01 Abbott Molecular).

Results

Patients were diagnosed with the following diseases caused by *Candida spp.*: CE was detected in 63% of patients, seborrheic dermatitis in 12%, fungal colitis in 2%. (Figures 1, *a, b, c*)

C. albicans was detected in 34,69%, *C.glabrata* - in 16.32%, and *C.krusei* – in 8.16% of patients. (Figure 2).

To study the effectiveness of antifungals against *Candida spp*. the sensitivity of the isolates to obtained Ketoconazole, Clotrimazol, Itraconazole, Fluconazole,Nystatin, Amphotericinum B from different biotopes was estimated by the disc diffusion method (Oxoid, Himedia).

The research results

A total of 84 isolates identified as *Candida spp.,* including *C.albicans, C. glabrata, C. tropicalis*, and *C. krusei. C. albicans* was dominated by abundance analysis of changes in the species composition of *Candida spp.* obtained in the study of smears from the oropharynx and intestines in 2015 and 2017 (Fig. 3).

The species composition of *Candida* fungi has changed by 2017 ($p<0.05$) by replacing *C. glabrata* (43.8% in 2015 and 10.8% in 2017) with *C. crusei* (0% in 2015 and 13.5% in 2017) and *C. tropicalis* (0% in 2015 and 18.9% in 2017).

In 2017, *C. tropicalis* was sown and the share of *C. albicans* and *C. krusei* increased (1.54 and 3.65 times,

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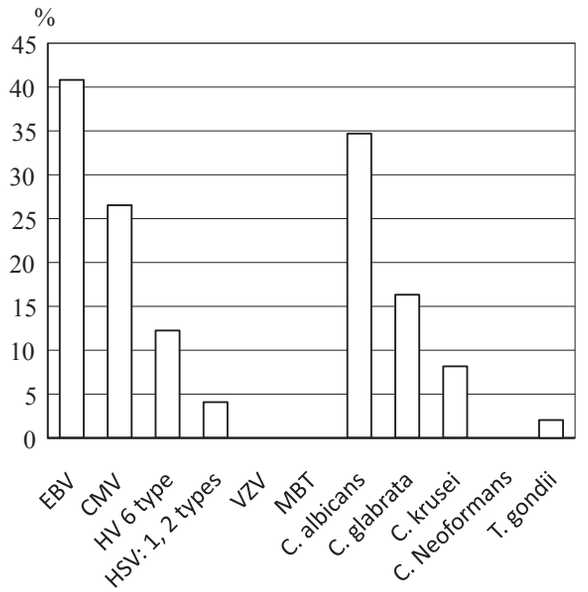

Figure 2. The frequency of detecting the genetic material of the causative agents of opportunistic infections in patients with HIV infection.

p>0.05, respectively). At the same time, the quantity of *C. glabrata* in 2017 was significantly reduced by 5.49 times (p<0.001).). Thus, from the data obtained by us it is clear that the species composition of *Candida* fungi has undergone a significant change in three years.

The number of isolates received from one patient increased by 1.5 times during the follow-up period - from 1.3 in 2015 to 1.95 in 2017, which demonstrates a tendency to form *Candida spp*. associations.

Efficiency of antimycotics of different pharmacological groups against *Candida spp.*, received from various biotopes (oropharynx, intestines) from HIV-infected patients.

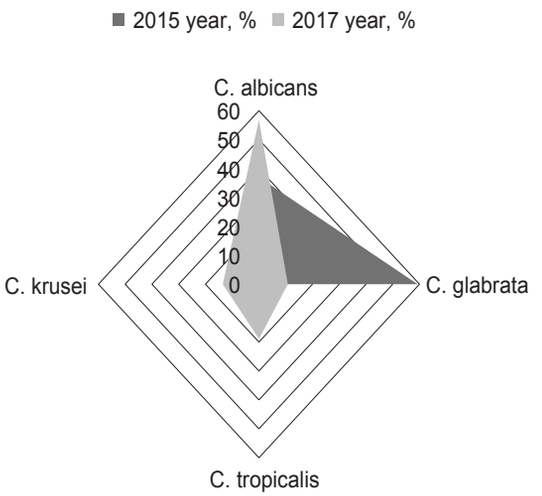

Figure 3. Changes in the spectrum of Candida fungi isolated from HIV-infected patients in 2015 and 2017.

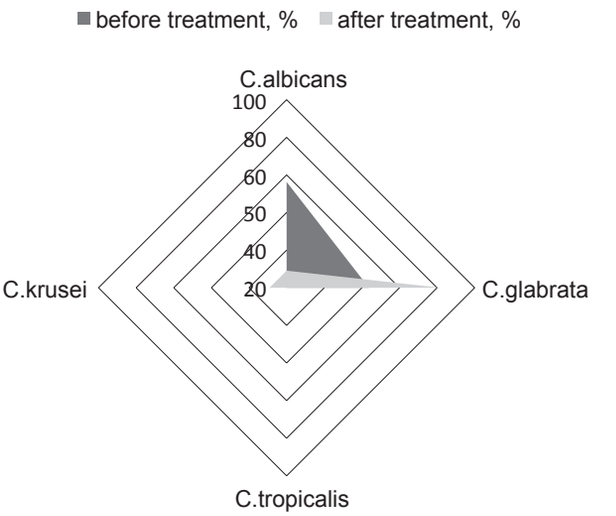

Figure 4. Changes in the spectrum of Candida fungi isolated from HIV-infected patients after 2 weeks of therapy with fluconazole

We thought it was clinically important to study changes in *Candida* species composition as a result of the use of flukonazole as the most common drug for the treatment of candidiasis (Fig. 4).

The analysis of the dynamics of species composition of *Candida* fungi showed a significant change in the course of treatment. There was a significant decrease in the *C. albicans* quantity by 6.18 times (p<0.05), an increase in the share of *C. glabrata* by 1.87 times (p<0.05), and the appearance of *C. krusei* in a single case.

The average number of isolates received from one patient was 1.29 in total. At the same time, in the course of treatment, this figure increased by almost 40%.

To study the effectiveness of antifungals against

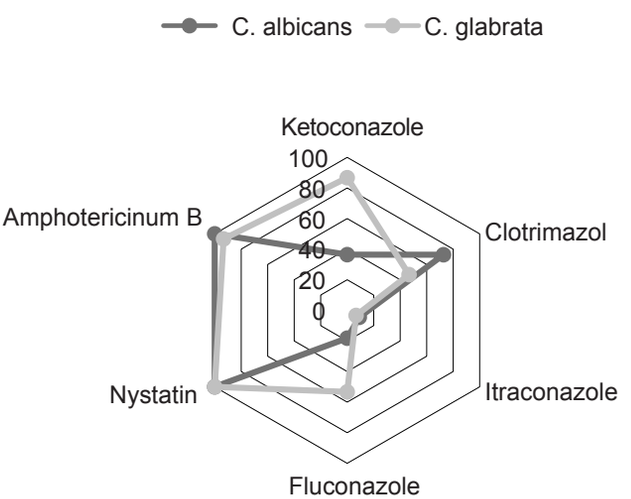

Figure 5**.** The effectiveness of antimycotics of different pharmacological groups against *Candida spp*. isolated from the oropharynx.

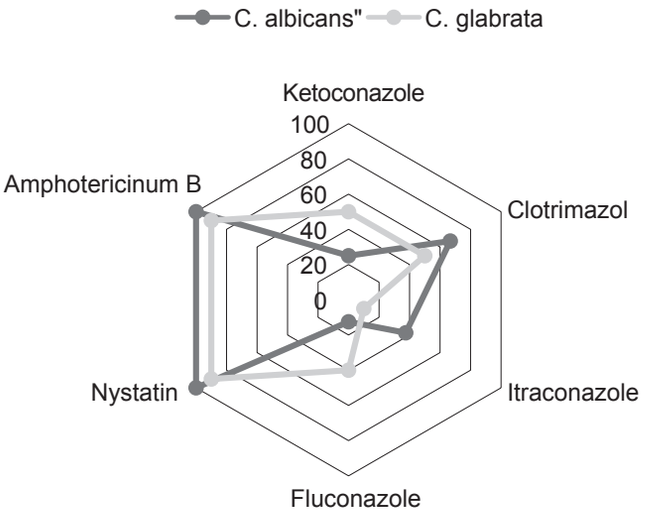

Figure 6. The effectiveness of antimycotics of different pharmacological groups against *Candida spp*. isolated from the intestine.

Candida spp. the sensitivity of the isolates obtained from different biotopes was estimated by the disc diffusion method (Fig. 5).

Almost all strains were sensitive to polyenes. *Candida spp*. isolates from the oropharynx in 100.0% of cases were sensitive to Nystatin.

The isolated strains were resistant to triazole derivatives. The maximum effect was shown by fluconazole against *C. glabrata* (53.3 %). The frequency of resistance to itraconazole exceeded 90% and was not related to species differences.

Strains, isolated from the intestine, also showed high sensitivity to polyenes and resistance to triazoles, but with respect to itraconazole it was expressed to a lesser extent (Fig. 6).

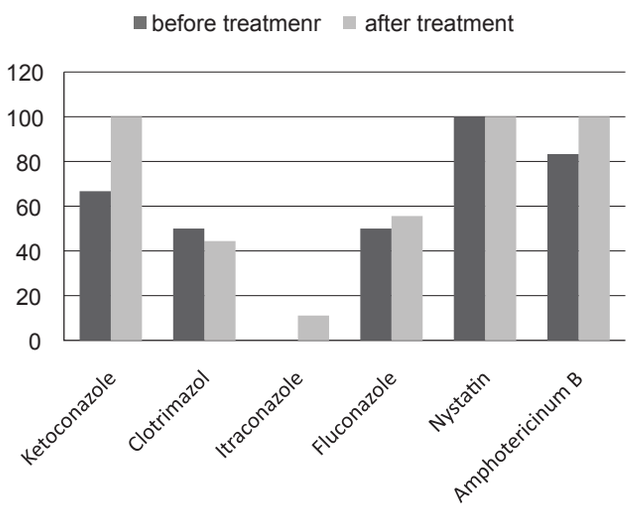

Figure 7**.** Drift in the sensitivity of fungi of *Candida* species isolated from the oropharynx to antimycotics after behavioral treatment.

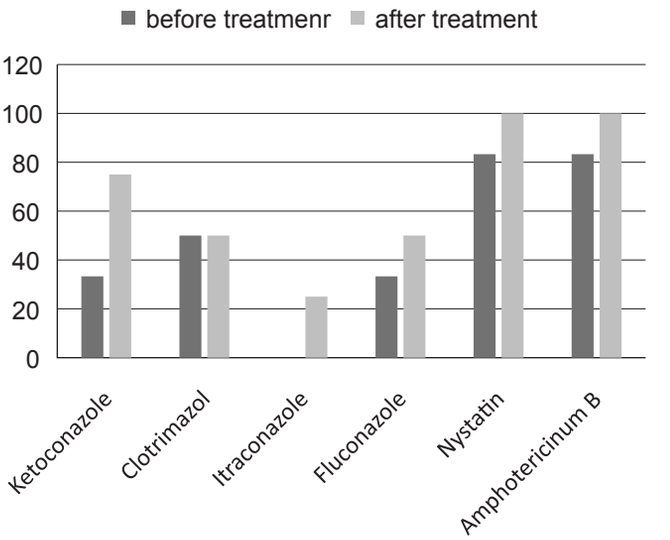

Figure 8. Drift of sensitivity of the isolated Candida fungi from the gastrointestinal tract to antimycotics after behavioral treatment.

It was of particular interest to study changes in the sensitivity of *Candida* fungi after the use of the most common drug for the treatment of candidiasis - Flukonazole (Fig. 7).

Evaluation of the sensitivity changes of the isolated strains to antimycotics revealed a significant increase in the sensitivity of Candida fungi to Itraconazole ($p<0.001$), but the sensitivity to other drugs has not changed significantly ($p>0.05$). High sensitivity of the studied strains to polyenes was established.

Candida spp. isolates from the oropharynx in 100.0% of cases were sensitive to Nystatin. Isolates obtained from the intestine also remained sensitive to polyenes (Fig. 8).

Discussion

Treatment of candidiasis in HIV-infected patients leads to changes in the species and strain composition of Candida. After eradication of *C. albicans* which is sensitive to fluconazole, more resistant strains of other species (*glabratae, krusei. tropicalis*) takes its place in the biotope, which is one of the reasons for the low effectiveness of antimycotic therapy.

In order to improve the effectiveness of anti-candidiasis therapy for HIV-infected patients, it is important to critically evaluate the template approach to the treatment of candidiasis of any location with azole-type drugs.

Conclusion

Treatment of candidiasis in HIV-infected patients leads to changes in the species and strain composition of Candida. After eradication of *C. albicans* which is sensitive to fluconazole, more resistant strains of other species (glabratae, krusei. tropicalis) takes its place in

the biotope, which is one of the reasons for the low effectiveness of antimycotic therapy.

In order to improve the effectiveness of anti-candidiasis therapy for HIV-infected patients, it is important to critically evaluate the template approach to the treatment of candidiasis of any location with azole-type drugs.

The regular monitoring of Candida drug sensitivity is of a particular importance, which will allow timely identification of the causes of inefficiency of drug therapy and correction of its schemes.

Individual selection of antimycotic therapy depending on the localization of the pathological process and microbiological characteristics of Candida strains seems clinically justified. In the case of superficial forms of candidiasis (including candidiasis glossitis / stomatitis), it is advisable to use Nystatin, to which the majority of strains are sensitive, or prescription of echinocandins in case of ineffectiveness of standard schemes. Thus, optimization of anti-candidiasis treatment for HIV-infection requires a flexible differentiated approach.

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