# COMPARATIVE ACTIVITY OF FLUCONAZOLE (FLU) AND VORICONAZOLE (VOR) AGAINST CANDIDA ISOLATES IN RUSSIA IN 2004 AND 2006

M-542


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## Abstract


Background. To compare in vitro activity of FLU and VOR against clinically significant *Candida* isolates in 2004 and 2006 in Russia.

Methods. Strains were tested with disk-diffusion method according M44-P CLSI guidelines and assessed with BIOMIC system within ARTEMIS Disk study. The 2004 data for VOR were limited to MIC (μg/mL) due to the absence of interpretive criteria, which were approved in 2005: susceptible - <=1 μg/mL, susceptible dose-depended - 2 μg/mL, resistant - <=4 μg/mL.

Results. A total of 2090 and 2458 strains were tested in 2004 and 2006, respectively. The major tested species for 2004/2006 were: *C.albicans* 1490/1917, *C.glabrata* 113/156, *C.krusei* 71/103, *Candida* spp. 100/77, *C.parapsilosis* 85/72, *C.tropicalis* 63/30, *C.kefyr* 44/26. The susceptibility data presented in Table 1.

Tab. 1. Susceptibility data for FLU and VOR.

| Species | FLU S(%) | | FLU SDD(%) | | VOR $MIC_{50}$ | | VOR $MIC_{90}$ | |
|---|---|---|---|---|---|---|---|---|
| | 2004 | 2006 | 2004 | 2006 | 2004 | 2006 | 2004 | 2006 |
| *C.albicans* | 96.6 | 96.2 | 0.3 | 0.2 | 0.02 | 0.02 | 0.01 | 0.12 |
| *C.glabrata* | 59.3 | 69.9 | 17.7 | 15.4 | 0.31 | 0.36 | 3.11 | 2.08 |
| *C.krusei* | 8.5 | 10.7 | 8.5 | 18.4 | 0.24 | 0.27 | 0.79 | 1.16 |
| *Candida spp.* | 81 | 84 | 2 | 13.6 | 0.05 | 0.10 | 1.14 | 0.85 |
| *C.parapsilosis* | 83.5 | 93.2 | 7.1 | 4.1 | 0.02 | 0.02 | 0.41 | 0.37 |
| *C.tropicalis* | 79.4 | 86.7 | 6.3 | 0 | 0.05 | 0.09 | 3.12 | 7.44 |
| *C.kefyr* | 97.7 | 96.2 | 2.3 | 3.8 | <.008 | 0.03 | 0.03 | 0.13 |

Conclusions. With the exception of *C.glabrata* and *C.krusei,* FLU remains highly active against *Candida* spp. with no temporal changes between 2004 and 2006. VOR retains high activity against all *Candida* spp., also a two times increased MICs for *C.tropicalis* in 2006 may be of some concern.


## Introduction

The problem of *Candida* resistance to azole antifungals is one of the most important problem in medical mycology. FLU is of the most widely used azole in treatment of candidiasis and other yeasts infections. That is why concerns about the development of resistance have been raised. VOR is a new extended-spectrum triazole has been approved for numerous indications including invasive *Candida* infections resistant to FLU. The main object of the study is to compare *in vitro* activities of FLU and VOR against clinical strains of yeasts using disk diffusion method.

## Materials and Methods

These data are interim data of the international multicenter antifungal surveilance program ARTEMIS Disk, sponsored by Pfizer Inc. A total of 8 Russian research centres participate in this study (see map). All research work was supervised by Institute of Antimicrobial Chemotherapy of Smolensk State Medical Academy.

Only clinically significant yeasts isolates were tested using disk diffusion method according M44-P CLSI protocol with 25 mcg FLU and 1 mcg VOR disks (Becton Dickinson and Company, USA) and standard Muller-Hinton media supplemented with 2% glucose and 0.5 mcg/ml methylene blue.

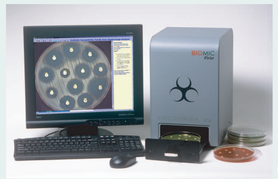

Next interpretative criteria were used for FLU and VOR:

| | Zone d (mm) | MIC (mcg/ml) | Zone d (mm) | MIC (mcg/ml) |
|---|---|---|---|---|
| Susceptible (S) | 19 | <=8 | >=17 | <=1 |
| Susceptible dose-depended (SDD) | 15-18 | 16-32 | 14-16 | 2-4 |
| Resistant (R) | 14 | >=64 | <=13 | >=6 |

The 2004 data for VOR were limited to MIC due to the absence of interpretive criteria (approved in 2005).

Quality control (QC) tests were performed using ATCC cultures: *C.albicans* ATCC 90028 (acceptable ranges for fluconazole 28-39 mm and for voriconazole 31-42 mm).

The final results were assessed with automatic plate-reading system BIOMIC, produced and supported with original software by Giles Scientific Inc. (Santa Barbara, CA, USA).




Taken from www.biomic.com

Zone diameter, susceptibility category (S, SDD or R), MIC and QC test results were recorded electronicaly. Patient and doctor names, duplicate test results (same patient-same species-same biotype result) and uncontrolled results were automaticaly eliminated prior to analysis.

## Results

A total of 2090 and 2477 of clinically significant yeast isolates were tested in 2004 and 2006, respectively. The distribution of tested isolates among centers is presented on the Figure 1.

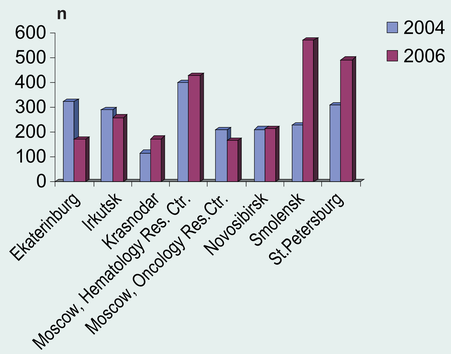



Figure 1. Distribution of isolates among centres

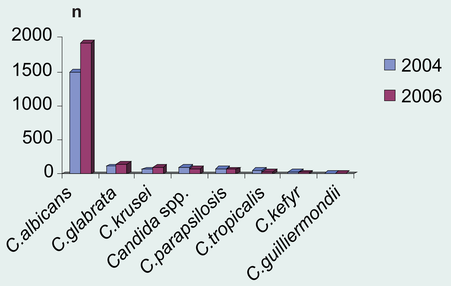



Figure 2. Distribution of main tested species

*C.albicans* was the most frequently isolated species - 71.2% in 2004 (n=1490) and 77.9% in 2006 (n=1917). The distribution of main species is on the Figure 2. All other species were few and there were no significant differences in their numbers between 2004 and 2006: *C.lusitaniae, C.norvegensis, C.famata, C.inconspicua,* and representatives of other yeasts, such as *Saccharomyces* spp., *Trichosporon* spp., *Pichia* spp., *Rhodotorula* spp., *Cryptococcus* spp.

FLU showed a good susceptibility level in both 2004 and 2006, except for *C.krusei* and *C.glabrata,* with no temporal changes. Moreover comparing 2004 and 2006 somewhat increased susceptibility of *C.glabrata* (59.3% vs. 69.3%), *C.paraspilosis* (83.5% vs. 93.2%) and *C.guilliermondii* (66.7% vs. 92.9%) strains was noted.

All tested strains were highly susceptible to VOR, with somewhat reduced activity against *C.glabrata,* but perfect activity against *C.krusei,* both in 2004 and 2006 with no temporal changes except for *C.tropicalis* - a two times increased MIC90 was found in 2006 comparing with 2004 (3.12 vs. 7.44). All susceptibility data for FLU and VOR are summarized in Table 2.

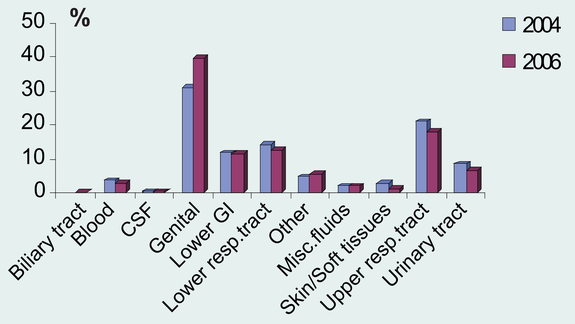



Figure 3. Specimen types distribution.

Table 2. Summarized susceptibility data for FLU and VOR

| Species ($n_{2004/2006}$) | FLU S(%) | | FLU SDD(%) | | VOR MIC 50 | | VOR MIC 90 | |
|---|---|---|---|---|---|---|---|---|
| | 2004 | 2006 | 2004 | 2006 | 2004 | 2006 | 2004 | 2006 |
| *C.albicans* (1490/1929) | 96.6 | 96.2 | 0.3 | 0.2 | 0.02 | 0.02 | 0.01 | 0.12 |
| *C.glabrata* (113/156) | 59.3 | 69.9 | 17.7 | 15.4 | 0.31 | 0.36 | 3.11 | 2.08 |
| *C.krusei* (71/103) | 8.5 | 10.7 | 8.5 | 18.4 | 0.24 | 0.27 | 0.79 | 1.16 |
| *Candida* spp. (100/81) | 81 | 84 | 2 | 13.6 | 0.05 | 0.10 | 1.14 | 0.85 |
| *C.parapsilosis* (85/73) | 83.5 | 93.2 | 7.1 | 4.1 | 0.02 | 0.02 | 0.41 | 0.37 |
| *C.tropicalis* (63/30) | 79.4 | 86.7 | 6.3 | 0 | 0.05 | 0.09 | 3.12 | 7.44 |
| *C.kefyr* (44/26) | 97.7 | 96.2 | 2.3 | 3.8 | <.008 | 0.03 | 0.03 | 0.13 |
| *C.guilliermondii* (18/14) | 66.7 | 92.9 | 16.7 | 7.1 | 0.14 | 0.12 | 1.65 | 0.59 |
| *C.famata** (10/9) | 7 | 6 | 1 | 1 | 0.03 | 0.06 | 0.77 | 0.94 |
| *C.lusitaniae** (6/9) | 6 | 9 | 0 | 0 | 0.01 | 0.02 | 0.05 | 0.22 |
| *C.norvegensis** (15/9) | 6 | 4 | 3 | 4 | 0.05 | 0.06 | 0.82 | 0.76 |
| *C.inconspicua** (11/8) | 6 | 1 | 1 | 1 | 0.05 | 0.16 | 0.53 | 0.33 |

* "n" instead of "%" in FLU columns

## Conclusions

1. *Candida albicans* remains the most prevalent species among *Candida* spp.
2. FLU and VOR have high in vitro activity against *C.albicans*
3. Except *C.glabrata* and *C.krusei,* FLU remains highly active against all other *Candida* species with no temporal changes between 2004 and 2006
4. VOR retains high activity against all *Candida* spp., also a two times increased MICs for *C.tropicalis* in 2006 may be of some concern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