Short thesis for the degree of doctor of philosophy (PhD)

In vitro and *in vivo* efficacy of caspofungin against *Candida albicans, Candida parapsilosis sensu stricto, Candida orthopsilosis* and *Candida metapsilosis* isolates

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Debrecen, 2014

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INTRODUCTION

The clinical importance of fungal infections was recognised in the second half of the last century which was closely associated with the spread of the invasive diagnostic and therapeutic devices. Candida species are considered to be the fourth most common nosocomial pathogens of bloodstream infections in the patient population of (general) hospitals. The most commonly isolated species are still *C. albicans* which is followed by *C. glabrata, C. parapsilosis, C. tropicalis* and *C. krusei.*

C. parapsilosis sensu lato causes serious nosocomial infections in most parts of the world and it is the second most commonly isolated *Candia* species causing bloodstream infections in South-America and the southern countries of Europe. In accordance with the studies of Tavanti and his researchers (2005), the three genotypes of *C. parapsilosis sensu lato* are three different species, *C. parapsilosis sensu stricto* (former I. genotype), *C. orthopsilosis* (former II. genotype), and *C. metapsilosi*s (former III. genotype).

C. parapsilosis, is a common saprophyte found on skin carried by health workers on their skin and under their nails. It is often found on catheters or intravenous feeding devices causing candidemia because its attachment capability and the biofilm evolving on the surface of intravascular devices. *C. orthopsilosis* was isolated from ascites, abcesses, catheters, cerebrospinal fluid, sputum and bronchus. *C. metapsilosi*s can also be isolated from abcesses, ascites, bronchus and synovial fluid.

More studies were found on the segregation of these three genetically close species in literature. At the time of the submission of our first study (May 2012) there was no information available in the international literature in relation with the *in vivo* efficacy of antifungals against all the three members of the "*psilosis*" group, apart from another study of ours being on report.

From *in vitro* data it was known that the members of the "psilosis" group differ from each other as far as their susceptibility to antifungals is concerned. The MIC values to echinocandins of *C. parapsilosis sensu stricto* were higher, while its MIC values to fluconazole were lower than that of the two other members of the group.

Echinocandins

Echinocandins (caspofungin, micafungin and anidulafungin) are the latest group of antifungals, and, at present, the first choice in case of the treatment of disseminated candidiasis. Echinocandins are non-competitive inhibitors of 1,3-β-D-glucan synthase, which is the essential component of fungal cell wall. The mammalian cell does not contain 1,3-β-D-glucan, therefore the efficacy of echinocandins is selective against fungi.

The MIC_{90} values of echinocandins against the members of the "*psilosis*" group are higher than that of the other four most commonly occurring species (*C. albicans, C. glabrata, C. tropicalis* és *C. krusei*). The reason for this is that, in case of all the three members of the "*psilosis*" group, in case of the 660^{th} amino acid, alanine substitutes proline in the Fks1

segment of glucan-synthase. In case of *C. othropsilosis*, isoleucine-valine replacement can also be observed in the hot spot region, although, its significance is not known yet.

According to Loui and his researchers' (2005) studies, the AUC/MIC value (area under the curve per MIC value) is the pharmacodinamic parameter which can be associated with the clinical efficacy of caspofungin. Their researches showed that caspofungin accumulates in internal organs as in reservoirs, and then it flows back to the blood.

Echinocandins are bound to proteins to a great extent, in case of caspofungin, it is 96%, in that of micafungin it is 99,8%, and in case of anidulafungin it is 99%. Based on conceptual considerations, because of the considerable protein binding, the echinocandin activity is to reduce against the different *Candia* species.

Antifungal susceptibility testing is done in RPMI-1640, while antifungals are effective in protein based medium (blood, tissues). Due to the effect of protein binding, free echinocandin concentration reduces; therefore much less drug is available for pathogen inhibition, so therapeutical failure can occur.

Not only does animal and human serum seem important in helping get to know the real effect of antifungals better, but they can also help reveal those resistant isolates that evolve during echinocandin therapy.

OBJECTIVES

Controversial information is available on the *in vivo* efficacy of echinocandins against *Candida parapsilosis sensu stricto,* and no data is available on against *Candida orthopsilosis* and *Candida metapsilosis.*

Our aims are to:

- comparing the *in vitro* efficacy of caspofungin in case of the three species in the "*psilopsis*" group in the standard RPMI-1640 and RPMI-1640 +50% in human serum test medium with the help of minimal inhibiting concentrations and time-kill curves.
- searching for a therapeutical alternative, in neutropenic mouse model, we compared the *in vivo* efficacy of caspofungin in animals at single daily low doses and in single large dose (using the same total dose)
- In every case, more caspofungin susceptible *Candida albicans* clinical isolates and one caspofungin resistant isolate were used.

MATERIALS AND METHODS

The origin of the used fungus species

The Hungarian stems were isolated and identified with traditional methods in the Diagnostic Laboratories at the Department of Microbiology at the University of Debrecen. A caspofungin resistant DPL20 (F645P) and two caspofungin susceptible *C. albicans* isolates were used. Based on our former results, the caspofungin showed fungistatic activity at ≤16 mg/l concentration against the two *C. parapsilosis sensu stricto* (896/1 and 9150), the CP25 *C. orthopsilosis* and the CP92 *C. metapsilosis* isolates. It showed fungicidal activity at ≥2 and 16 mg/l concentration against the CP85 and CP125 *C. orthopsilosis* isolates. Caspofungin also showed fungicidal activity at ≥1 and ≥8 mg/l concentration against the CP5 and CP86 *C. metapsilosis* isolates.

In vitro susceptible studies

The determination of the MIC values of caspofungin was accordance with the CLSI (Clinical and Laboratory Standards Institute) M27-A3 document in RPMI-1640 and RPMI-1640 plus 50% human serum (male, AB type, Sigma, Budapest) test medium with concentration ranged between 0.06-32 mg/l.

Plotting the time-kill curves in RPMI-1640 plus 50% human serum

Fungus suspension of 10^5 CFU/ml starting inoculum was made from fungus isolates in RPMI-1640 plus 50% test medium. The added caspofungin concentration was 0.5-16 x MIC values. As the 100, 150 and 200 mg daily doses with humans cause peak concentrations at 21.5-40.6 mg/l, therefore the highest concentration tested was 32 mg/l.

100-100 µl fluid was removed from the tubes after 0, 4, 8, 12, 24 and 48 hours and serially diluted tenfold in physiological saline solution, then 4x30 µl was plated onto Sabouraud dextrose agar. After 48 hours, the viable cell count was determined with the dilution data. The drug is considered fungicide if there is a 99.9% (3-$\log_{10}$) reduction in viable cell count compared to the starting inoculum.

In vivo studies I.

Our experiments were carried out with BALB/c type male mice, of which weight was 23-25 gram. Their keeping was in accordance with the “Care and Use of Laboratory Animals” directive. The mice were divided into groups, in the different groups their number varied between 7 and 9. Experimental authorization number: 10/2008 DE MÁB.

The development and upkeep of the continuous neutropanic state was attained with cyclophosphamide administration (four times during the experiment).

Infection of the mice

On the fourth day after their immunosuppression, the mice were infected through their veins on their tails' side, (0.2 ml/mouse). In case of *C. albicans* isolates, the inoculum of the vaccine was $8x10^4$ CFU/mouse, while in case of the "*psilosis"* group it was $6x10^6$ CFU/mouse.

Antifungal Treatment

The mice were treated with 1.2 and 5 mg/kg caspofungin (Cancidas®). The treatment started on the second day after the vaccination, the mice were given the doses in a volume of 0.5 ml in the abdominal cavity. The control group was given physiological saline solution.

Quantitative inoculum determination

On the seventh day the mice were killed with cervical dislocation, and both kidneys were removed. The kidneys were homogenized and suspension was made with one-millilitre sterile physiological saline solution. The logarithm of inoculums obtained from the kidneys was represented depending on the doses.

Statistical data analysis

In case of the kidney tissue burden on culture medium, Kruskal-Wallis test was used for significance calculation. $P<0.05$ value was considered significant.

In vivo studies II.

The experimental design is similar to the first chapter, therefore only the differences are mentioned here.

The experiments were carried out with BALB/c type female mice (19-21 gram). In case of every isolates, four mice were dissected before the treatment, and the kidney tissue burden was determined in order that more information could be gathered about the efficacy of the treatments. In this experiment, the *in vivo* efficacy of the single large dose caspofungin was studied; therefore, in the same total dose, the efficacy of the daily lower dose was also studied. The mice were given 1, 2 and 3 mg/kg daily doses and 5, 10 and 15 mg/kg single doses intraperitoneally for five days in case of *C. albicans* (17433, 10920), *C. orthopsilosis* (CP85, CP125) and *C. metapsilosis* (CP5, CP86) isolates. 3 and 4 mg/kg daily doses and 15 and 20 mg/kg single doses were given in case of *C. parapsilosis sensu stricto* (896/1, 9150) isolates. In case of resistant *C. albicans* (DPL20) isolate, 4 and 6 mg/kg daily and 20 and 80 mg/kg single doses were used.

RESULTS

Results of minimal inhibitory concentration in RPMI-1640

Based on the species-specific breakpoints, the C. albicans (MIC=0.015 mg/L) and the *C. parapsilosis sensu stricto* (MIC=1 mg/L) clinical isolates were susceptible to caspofungin in RPMI-1640 culture medium, while the DPL20 isolate (MIC=4mg/L) was resistant. In case of *C. orthopsilosis* (MIC=0.12mg/L) and *C. metapsilosis* (MIC=0.25-0.5mg/L) isolates, species-specific breakpoints are not determined, although, except for, CP92 isolate, in case of *C. albicans*, the 0.25mg/l value was not surpassed.

Results of minimal inhibitory concentration in RPMI-1640 plus 50% serum medium

In case of all the four studied species, the MIC values increased 2-32-fold in 50% human serum test medium compared to the one measured in RPMI-1640. In case of *C. albicans* and *C. parapsilosis sensu stricto* isolates, the MIC values were 0.25 mg/L and 8 mg/L. In case of *C. orthopsilosis*, they were 2-4, while in case of *C. metapsilosis*, the MIC values increased to 1-4 mg/L.

Results of the time-kill experiments in RPMI-1640 plus 50% serum medium

Every isolate developed well in RPMI-1640 plus 50% serum. The time-kill curves showed similar shape to that of the control curves at 0.5x MIC values in case of every isolate of the four species, so inhibitory effect is not observed. Caspofungin, independently of species, showed fungistatic activity against every isolate at 1-2xMIC values. Compared to the starting inoculum, the decrease was 1.35-2.67 log CFU/ml in case of *C. albicans*, while in case of *C. parapsilosis sensu stricto* it was 0,05-1,41 log CFU/ml.

In case of *C. orthopsilosis* isolates, after 24 hours fungicide activity was observed at 8-16x MIC (16-32mg/l) values, while after 48 hours it was at 2-3x MIC (4-8mg/l) values. Similar time-kill curves were observed in case of *C. metapsilosis* isolates.

Results of in vivo susceptibility studies I.

In vivo efficacy of caspofungin against *C. albicans*

All the three caspofungin doses decreased the kidney tissue fungal burdens with 2 units ($P<0.001$-0.05) against both clinical isolates.

In vivo efficacy of caspofungin against *C. parapsilosis sensu stricto*

Only the largest caspofungin dose (5mg/kg) proved to be effective (P0.001-0.01) against both clinical isolates, although the daily 2mg/kg dose was also effective ($P<0.05$) against the 896/1 isolate.

In vivo efficacy of caspofungin against *C. orthopsilosis*

The daily 1 mg/kg dose did not decrease significantly the kidney tissue fungal burdens in either of the cases, although the 2 and 5 mg/kg doses were proved to be effective in every case ()P<0,001-0,05).

In vivo efficacy of caspofungin against *C. metapsilosis*

The results are similar to that of the ones got in case of *C. orthopsilosis,* although the daily 5mg/kg doses decreased kidney tissue fungal burdens with at least 2 units.

Results of *in vivo* susceptible studies II.

Starting inoculums at the beginning of the treatment

The starting inoculums, in case of each species, was similar, in spite of the fact that the mice infected with *C. albicans* isolates were given a significantly lower dose during the venous infection. In case of *C. albicans* 8,1 x 10^4-7,4 x 10^5, in case of *C. parapsilosis sensu stricto* 8,5 x 10^4-4,7 x 10^5, in case of *C. orthopsilosis* 3,9 x 10^5-1,5 x10^6, while in case of *C. metapsilosis* 9,1 x 10^4-7,7 x 10^5 CFU/gram was the kidney tissue burden obtained from control mice at the beginning of the treatment. In case of *C. albicans*, *C. orthopsilosis* and *C. metapsilosis* isolates, by the end of the treatment period, the increase was 1 unit larger but 2 units smaller in the kidneys in case of the control mice. In case of the two *C. parapsilosis sensu stricto* and the DPL20, echinocandin resistant *C. albicans* isolates, the increase was smaller than one unit.

In vivo efficacy of caspofungin against *C. albicans*

Against clinical isolates all the six treatments significantly reduced the kidney tissue burden compared to day 6 control (P<0.05-0.01), although compared to day 1 control only minimal decrease, much less than 1 unit, occured. During each treatment there was no statistically significant difference (P>0.05). In case of DPL20 isolate, there was no effective dose (P>0.05). Moreover, in case of every treatment regimen, increase was observed compared to day 1 control, even case of the largest doses.

In vivo efficacy of caspofungin against *C. parapsilosis sensu stricto*

In case of both clinical isolates the 3mg/kg dose did not but the 4 mg/kg, the 15mg/kg and the 20 mg/kg daily doses significantly decreased the kidney tissue burden (P<0.05-0.01).

In vivo efficacy of caspofungin against *C. orthopsilosis*

Against CP85 isolate, the smallest daily dose (1mg/kg) and with this correspondent single dose (5mg/kg) were not effective, although the other treatment regimen significantly reduced the kidney tissue fungal burden ($P<0.005$-0.001). The 3mg/kg daily and 15 mg/kg single doses compared to day 1 control decreased the kidney tissue burden with at least one unit. In case of CP150 isolate, the 3 mg/kg daily and the 10 and 15 mg/kg single daily doses were significantly effective only ($P<0.05$-0.001).

In vivo efficacy of caspofungin against *C. metapsilosis*

All doses applied, except for the daily 1 mg/kg, with the CP86 isolate, significantly reduced the kidney tissue fungal burden. Compared to day 1 control, less-than-one-unit decrease was observed. Among each therapeutical dose no significant difference was observed ($P>0.05$).

DISCUSSION

The invasive *Candida* infections cause significant problems in different medical institutions, prolonging hospitalisation; and despite the significant cost increase, mortality is rather high. The most common *Candida* species is still *C. albicans*, although the number of *C. albicans* causing invasive infections has not been increased in the last 3 decades. It can be contributed to the introduction of fluconazole in 1991, as well as, that of echinocandin and caspofungin in therapeutic regimen 10 years ago.

The *in vivo* and *in vitro* susceptibility of the most virulent (*C. albicans*) and least virulent (*C. parapsilosis) Candida* species were studied to the earliest introduced caspofungin. We studied how much MIC values measured in RPMI-1640 increase in RPMI-1640 plus 50% serum; and how large the killing activity of caspofungin against *C. albicans* and the "*psilosis*" group. The same studied isolates were tested in two different therapeutic neutropenic mouse models, while correlation was searched between *in vivo* and *in vitro* results.

In case of *C. albicans* isolates, the MIC values in RPMI-1640 serum medium increased, although at low (≥0.25mg/l) concentrations excellent fungistatic activity was observed in time-kill experiments. Our *in vivo* results largely correlate with the in vitro results, since the 1 mg/kg daily dose against both isolates significantly reduced the kidney tissue burden in both experiments. As the pharmacodynamic target is the same in the laboratory animals and in humans, we can expect the same *in vivo* efficacy in humans and animals, as well, if the area under the curve and the peak concentrations match. The 1 mg/kg daily dose causes 3.6-5.04 mg/l peak concentrations and 35,49-53.59 mg·h/l area under the curve (AUC). The 1 mg/kg daily dose applied in mouse study equals with 35 mg/kg dose in humans, which causes 5.97 mg/l peak concentrations and 54.9 mg·h/l area under the curve (AUC). Thus, the 2 and 5 mg/kg doses applied in mice equal with 50-milligram and 70-milligram dose in humans.

Single large dose treatments were also chosen so that the areas under the curve and/or C_{max} values could be similar. In accordance with these, the 5, 10 and 15 mg/kg single doses were as effective against 10920 and 17433 *C. albicans* as the daily 1, 2 and 3 mg/kg doses. Our results equal with the similar experimental models found in literature. It is significant that only little inoculum decrease was observed compared to day 1 control. This result calls attention to that, in case of neutropenic individuals, the echinocandin therapy may not eliminate the pathogen, accordingly, only fungistatic activity can be attained during the treatment. Thus, at the time of premature discontinuation of the normal dose treatment a lot of pathogens can be found in the internal organs which start growing rapidly in lack of antifungals causing patient's death.

In case of echinocandin resistant, homozygous mutant DPL20, neither of the doses were effective; moreover, compared to day 1 control, increase was observed in case of any therapeutical regimen. Compared to the two susceptible isolates the viable cell count obtained from control mice was lower indicating smaller virulence compared to the two other (wild) isolates.

The *in vitro* activity of caspofungin against the "*psilosis*" group reduced in 50% serum, as the MIC values and time-kill curves show. The results at clinically attainable caspofungin in serum, mainly in case of *C. parapsilosis sensu stricto*, question the *in vivo* efficacy of caspofungin, although, in case of the 4 mg/kg daily doses in mice, 16-18.4 mg/l C_{max} values are measured. The 5 mg/kg daily dose was effective in case of both isolates (in humans it is 70mg). Our first *in vivo* experimental design confirms the results in accordance with which caspofungin can be effective against the "*psilosis*" group even in neutropenic infection, as well.

In the second experimental design, the most significant result against the "*psilosis*" group is that, in case of the same total dose, caspofungin was more effective in single large dose than in daily low dose. The reason for this may be the following:

The unique pharamcokinetics of echinocandins makes it possible for the internal organs to work as reservoirs after the intravenous treatment. It is known from previous studies that caspofungin flowing back from tissues to blood has an important role in providing continuous high level of echinocandins. In spite of the fact that caspofungin is largely protein bound in the serum, not only does the serum level of blood have the most important role in clinical efficacy but caspofungin also has even in bound form found in tissues. It is essential for pathogen elimination since there are not only different pathogens in blood but they can also enter any of the internal organs causing disseminated infection which is more severe than that if the pathogen was in blood only. Therefore, serum has to be present in tissues, as well. In case of single large dose administration, the C_{max} value is higher and the area under the curve (representing the total dose) evolves much sooner. As, in case of a five-day administration, the smaller daily dose given for the 4^{th} and the 5^{th} times is not sure to be able to provide full contribution to the formation of the area under the curve (AUC), therefore, the single large dose caspofungin is more effective against the "*psilosis*" group in case of the same total dose compared to the smaller, daily dose. The clinical efficacy of the single, large dose echinocandin administration is less known. The current studies in this topic are mainly about the prophylactic administration of echinocandins and the single, large dosage echinocandin therapy shows the same clinical efficacy as the daily, smaller dosage therapy.

In the targeted and empirical therapy of invasive candidiasis, echinocandins have currently the biggest role. Because of the clinical symptoms and the anamesis, there should be reasonable suspicion of fungal infection in case of patients with high risk factor, thus, after the proper sampling (blood, throat secretion, wound secretion), therapy is to be started based on fluconazole or one of echinocandins. The *in vivo* efficacy of echinocandins against all *Candida* species and only few side effects make the single, large dose or the daily, large dose possible.

However, echinocandins are not the first choice against *C. parapsilosis sensu stricto*, the newest recommendations suggest the continuation of echinocandin administration during empirical therapy, even if the patient improved clinically. Therefore, it is very important to

have proper *in vitro* and *in vivo* experiments available to predict the efficacy of echinocandin therapy.

SUMMARY

In our study we determined the *in vitro* and *in vivo* activity of caspofungin against the three species of the "*psilosis*" group (*Candida parapsilosis sensu stricto, Candida orthopsilosis* and *Candida metapsilosis*) and the most virulent *C. albicans.*

The *in vitro* activity of caspofungin decreased 2-32-fold in RPMI-1640 plus 50% human serum test medium compared to RPMI-1640 in accordance with results after the increase of MIC values and the plotting of time-kill curves. In neutropenic mouse model, the daily 1 mg/kg caspofungin dose was effective against *C. albicans,* the daily 2 mg/kg against *C. orthopsilosis* and *C. metapsilosis,* and the daily 5 mg/kg against *C. parapsilosis sensu stricto* isolates. In case of *C. albicans,* the efficacy of the 5, 10 and 15 mg/kg single caspofungin doses was not worse than that of the 1, 2 and 3 mg/kg daily doses, but in case of the caspofungin resistant isolate the 16 mg/kg daily and even the 80 mg/kg single doses were ineffective. In case of *Candida parapsilosis sensu stricto,* the 15 and 20 mg/kg single and the 4 mg/kg daily doses were effective. The 10 and 15 mg/kg single and the 3 mg/kg daily doses against *C. orthopsilosis,* while the 5, 10 and 15 mg/kg single and the 2 and 3 mg/kg daily doses against *C. metapsilosis* significantly reduced the kidney tissue burden.

Confirming our previous knowledge on *C. albicans,* the *in vivo* efficacy of the single, large dose caspofungin is not worse than that of the smaller, daily dose caspofungin in the same total dose. However, in case of the "*psilosis*" group, the single, large dose caspofungin was several times more effective than the daily smaller doses (in case of the same dose), further studies are needed to decide whether it is worth using the single, large dose echinocandin in the treatment of patients suffering from candidemia.

Register number: DEENKÉTK/196/2014.
Item number:
Subject: Ph.D. List of Publications

Candidate: Réka Berényi
Neptun ID: J4KQE8
Doctoral School: Doctoral School of Pharmaceutical Sciences

List of publications related to the dissertation

1. **Berényi, R.**, Kovács, R., Domán, M., Gesztelyi, R., Kardos, G., Juhász, B., Perlin, D., Majoros, L.: Efficacy of single large doses of caspofungin in a neutropenic murine model against the "psilosis" group.
New Microbiol. 37 (3), 355-362, 2014.
IF:1.603 (2013)

2. Földi, R., Kovács, R., Gesztelyi, R., Kardos, G., **Berényi, R.**, Juhász, B., Szilágyi, J., Mózes, J., Majoros, L.: Comparison of In Vitro and Vivo Efficacy of Caspofungin Against Candida parapsilosis, C. orthopsilosis, C. metapsilosis and C. albicans.
Mycopathologia. 174 (4), 311-318, 2012.
DOI: http://dx.doi.org/10.1007/s11046-012-9554-7
IF:1.489

List of other publications

3. Kovács, R., Gesztelyi, R., Perlin, D.S., Kardos, G., Domán, M., **Berényi, R.**, Majoros, L.: Killing rates for caspofungin against Candida albicans after brief and continuous caspofungin exposure in the presence and absence of serum.
Mycopathologia. "accepted by publisher" (2014)
DOI: http://dx.doi.org/10.1007/s11046-014-9799-4
IF:1.545 (2013)

4. Kovács, R., Gesztelyi, R., **Berényi, R.**, Domán, M., Kardos, G., Juhász, B., Majoros, L.: Killing rates exerted by caspofungin in 50 % serum and its correlation with in vivo efficacy in a neutropenic murine model against Candida krusei and Candida inconspicua.
J. Med. Microbiol. 63 (2), 186-194, 2014.
DOI: http://dx.doi.org/10.1099/jmm.0.066381-0
IF:2.266 (2013)

5. Földi, R., Szilágyi, J., Kardos, G., **Berényi, R.**, Kovács, R., Majoros, L.: Effect of 50% human serum on the killing activity of micafungin against eight Candida species using time-kill methodology.
Diagn. Microbiol. Infect. Dis. 73 (4), 338-342, 2012.
DOI: http://dx.doi.org/10.1016/j.diagmicrobio.2012.05.011
IF:2.26

Total IF of journals (all publications): 9,163
Total IF of journals (publications related to the dissertation): 3,092

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

28 August, 2014

Posters

R. Kovács, R. Gesztelyi, **R. Berényi**, M. Domán, G. Kardos, B. Juhász, L. Majoros Should echinocandin doses be increased against Candida species? An *in vitro* and *in vivo* study of caspofungin against *Candida albicans*, *C. krusei* and *C. inconspicua*. 6th Trends in Medical Mycology, 11-14 October 2013. Coppenhagen, Denmark (P011) Mycoses

L. Majoros, R. Kovács, **R. Berényi**, M. Domán, C. Miszti and G. Kardos Effect of 50% human serum ont he killing activity of micafungin against *C. dubliniensis*, *C. lusitaniae*, *C. guilliermondii* and *C. kefyr* using time-kill methodology. 6th Trends in Medical Mycology, 11-14 October 2013. Coppenhagen, Denmark (P021) Mycoses

Berényi Réka, Földi Richárd, Szilágyi Judit, Kardos Gábor, Kovács Renátó, Majoros László: Effect of 50% human serum on the killing activity of micafungin against eight *Candida* species using time-kill methodology V. Magyar Mikológiai Konferencia 2012. május 23-25. Budapest Magyarország

R. Földi, J. Szilágyi, R. Kovács, **R. Berényi**, G. Kardos, L. Majoros Effect of 50% human serum on the killing activity of micafungin against eight *Candida* species using time-kill methodology. 2nd workshop Medical Mycology: From basix science to clinical needs. December 8-10. 2011, Vienna, Austria (poster: PP-13)

L. Majoros, R. Kovács, **R. Berényi**, J. Szilágyi, R.Földi, R. Gesztelyi, G. Kardos, B. Juhász *In vitro* and *in vivo* efficacy of caspofungin against *Candida parapsilosis*, *C. orthopsilosis*, *C. metapsilosis* and *C. albicans*. 2nd workshop Medical Mycology: From basix science to clinical needs. December 8-10. 2011, Vienna, Austria (poster: S6-02)

Conference presentations

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