Antifungal susceptibility of dermatophytes isolated from patients with chronic renal failure

Perfil de suscetibilidade a antifúngicos de dermatófitos isolados de pacientes com insuficiência renal crônica

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Abstract: BACKGROUND: The prevalence of dermatophytosis in the general population is high, particularly in patients with chronic renal failure. Treatment requires the use of topical and/or systemic antifungal drugs. The efficacy of antifungal agents for the treatment of dermatophytosis has yet to be evaluated. Studies evaluating the in vitro activity of antifungal agents are rare, particularly in filamentous fungi.
OBJECTIVE: To evaluate the susceptibility profile of different species of dermatophytes isolated from patients with chronic renal failure to nine antifungal drugs available on the market for the treatment of dermatophytosis.
METHODS: Twenty-six isolates of dermatophytes obtained from patients with chronic renal failure were analyzed with respect to their susceptibility to nine antifungal agents (ketoconazole, ciclopirox olamine, fluconazole, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole), using the broth microdilution method proposed by the Clinical and Laboratory Standards Institute (CLSI) and adapted for dermatophytes.
RESULTS: Of the antifungal agents tested, the best results in terms of sensitivity were found with terbinafine and tioconazole, while the antifungal activity of fluconazole was found to be weak, particularly against strains of M. gypseum. Ciclopirox olamine, although less effective than terbinafine, also yielded satisfactory results.
CONCLUSIONS: In general, the sensitivity profile of the antifungal agents tested in this study was similar to results obtained in previous studies, confirming the need to determine which species is causing the dermatophytosis given that antifungal susceptibility varies from one species to another. Furthermore, the present findings show the importance of conducting in vitro sensitivity tests, since the sensitivity profile may differ among isolates of the same species.
Keywords: Antifungal agents; Arthrodermataceae; Kidney failure chronic; Mycoses

Resumo: FUNDAMENTOS: As dermatofitoses apresentam alta prevalência na população em geral e, principalmente, em pacientes com insuficiência renal crônica, necessitando tratamento com antifúngicos tópicos e/ou sistêmicos, cuja eficácia precisa ser avaliada. Estudos *in vitro* para avaliar a ação de antifúngicos são raros, especialmente, em fungos filamentosos.
OBJETIVO: Avaliar o perfil de suscetibilidade de diferentes espécies de dermatófitos, isolados de pacientes com insuficiência renal crônica, em relação a nove antifúngicos disponíveis comercialmente para o tratamento de dermatofitoses.
MÉTODO: Analisaram-se 26 isolados de dermatófitos de pacientes com insuficiência renal crônica em relação a nove antifúngicos (cetoconazol, ciclopirox olamina, fluconazol, griseofulvina, itraconazol, miconazol, piroctona olamina, terbinafina e tioconazol) pelo método de microdiluição em caldo proposto pelo *Clinical and Laboratory Standards Institute* (CLSI), com modificações para dermatófitos.
RESULTADOS: Entre os antifúngicos testados, a terbinafina e o tioconazol obtiveram os melhores resultados de sensibilidade e o fluconazol apresentou baixa atividade, especialmente para as amostras da espécie *M. gypseum*. O ciclopirox olamina, apesar de menos eficaz que a terbinafina, também mostrou resultados satisfatórios.
CONCLUSÕES: De modo geral, o perfil de sensibilidade dos antimicóticos testados seguiu o padrão de resultados mostrados por estudos anteriores, ratificando a necessidade de conhecimento da espécie causadora de dermatofitose, devido à variação do perfil de suscetibilidade entre as espécies. Além disso, nossos resultados demonstram a importância da realização de ensaios de sensibilidade *in vitro*, pois alguns isolados da mesma espécie apresentaram diferente perfil de sensibilidade.
Palavras-chave: Antimicóticos; *Arthrodermataceae*; Insuficiência renal crônica; Micoses

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INTRODUCTION

Dermatophytes are a group of closely related fungi capable of invading keratinized tissues such as the skin, hair, body hair and nails, causing infections referred to as dermatophytosis. [1] Epidemiological studies show that this pathology is among the most prevalent in the world and is considered the second most common skin disease in the adult population. [2] It is estimated that 10-15% of the general population may be affected by these microorganisms at some time in their lives. [3,4]

More than 30 species of dermatophytes have been identified; however, the great majority can be taxonomically classified into three anamorphic types: *Trichophyton*, *Microsporum* and *Epidermophyton*. The species most commonly reported as being the cause of infection in humans are *Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum canis, Trichophyton tonsurans* and *Epidermophyton floccosum*. The geographical distribution of these species varies greatly depending on the socioeconomic, hygienic and environmental conditions of the population. [4-6]

The risk factors associated with dermatophytoses include aging, immunosuppression, a family history of diabetes mellitus, peripheral vascular disease, skin-related disorders such as hyperhidrosis and psoriasis, the use of tight-fitting footwear and trauma to the nails. [7] Studies have shown that patients with chronic renal failure are more susceptible to dermatophytosis, principally onychomycosis, which is the second most common disorder in patients undergoing hemodialysis, with a prevalence that ranges from 6.2 to 69.8%. [7-9] Onychomycosis is one of the most difficult dermatological conditions to treat and according to some authors therapeutic failure ranges from 20% to 50%. [10,11]

The choice of the most appropriate treatment is determined by the site and extent of the infection, by the species involved and by the efficacy, safety profile and kinetics of the available drugs. Treatment may be carried out with the use of topical agents such as imidazole antimycotics, including tioconazole and miconazole, and griseofulvin, resulting in therapeutic success in 75% of cases. [12] Studies indicate that the topical application of ciclopirox olamine may represent an alternative treatment for superficial fungal infections, particularly when used in combination with other antifungal medications such as amorolfine, salicylic acid and ketoconazole. [13-15] Oral treatment with antifungal agents such as terbinafine, itraconazole, ketoconazole and fluconazole constitutes the treatment of choice for dermatophytoses that fail to respond to topical therapy. [16]

The spectrum of activity of these antifungal agents varies and this may result in treatment failure, possibly due to poor compliance by patients, lack of penetration of the drug, the bioavailability of the medication, drug interactions or resistance. [17] In vitro analysis of the antifungal activity of these drugs permits comparison between different antifungal agents and may help in selecting an effective method of treatment for patients affected by these infections. Therefore, the objective of the present study was to evaluate the susceptibility profile of different species of dermatophytes isolated from patients with chronic renal failure to new antifungal agents commercially available for the treatment of dermatophytosis.

MATERIALS AND METHODS

Microorganisms

Twenty-six clinical isolates of dermatophytes (4 *Microsporum canis,* 7 *Microsporum gypseum*, 4 *Trichophyton interdigitale*, 8 *Trichophyton mentagrophytes* and 3 *Trichophyton rubrum*) from patients with chronic renal failure receiving care at the dermatology outpatient clinic of the *Santa Casa de Porto Alegre* Hospital Complex were admitted to the present study and subjected to direct mycological examination and culture. Following identification of the species, the cultures were maintained in Sabouraud-dextrose agar (Difco, Detroit, MI, USA), immersed in mineral oil (União Química, São Paulo, Brazil) at room temperature.

Antifungal activity in vitro

Antifungal susceptibility testing was conducted in accordance with the broth microdilution method proposed in protocol M38-A of the Clinical and Laboratory Standards Institute (CLSI) and adapted for dermatophytes. [18] Nine commercially available antifungal agents recommended for the treatment of dermatophytosis were used: ketoconazole (Química Farmacêutica, Bayer, Barcelona, Spain), ciclopirox olamine (Aventis, Dermik Laboratories, Berwyn, PA, USA), fluconazole (Sigma, St. Louis, MO, USA), griseofulvin (Schering-Plough, Rio de Janeiro, Brazil), itraconazole (Jansen-Cilag, São Paulo, Brazil), miconazole (Jansen-Cilag, São Paulo, Brazil), piroctone olamine (IFFECT, CHEMPHAR, China), terbinafine (Novartis Research Institute, Vienna, Austria) and tioconazole (Pfizer Inc., New York, USA).

The stock solution of antifungal agents was prepared in dimethyl sulfoxide (DMSO; Vetec, Brazil) and dilutions were later made in RPMI 1640 medium (Sigma, St. Louis, MO, USA) buffered at pH 7.0 with 165 mM of 3-(N-morpholino)propanesulfonic acid (MOPS; Sigma) to obtain concentrations of 0.25 to

128 g/ml for fluconazole and 0.03 to 16 μg/ml for the other antifungal agents.

The clinical isolates were then inoculated in potato dextrose agar (Difco, Detroit, MI, USA), with the addition of 2% rice flour (Maninho, Brazil) and maintained at 28°C for seven days. The suspension of spores from each culture was prepared in 0.89% saline solution and adjusted in a spectrophotometer (Spectrum Instruments Co, Shanghai, China) until reaching cell density with transmittance of 80-82% at 520 nm. The inoculum was diluted at a proportion of 1:50 in RPMI-MOPS broth.

The assay was performed using sterile, 96-well plates with a U-shaped base into which 100 μl were added of each antifungal concentration to be tested. Next, 100 μl aliquots of the 1:50 dilution of the inoculum were added to each one of the wells. The final concentration of microorganisms achieved was 5×10^3 to 5×10^4 colony-forming units (CFUs)/ml. An antifungal-free control (growth control) and a control containing no organisms (sterility control) were included in these tests. The plates were incubated at 28°C for three days. *Candida parapsilosis* American Type Culture Collection (ATCC) 22019 and *C. krusei* ATCC 6258 were used as methodology controls.

Minimum inhibitory concentration (MIC) was determined visually by comparing the test with the growth of the drug-free control. MIC was defined as the lowest concentration of the drug capable of completely inhibiting fungal growth in the case of itraconazole and terbinafine and capable of inhibiting 80% of growth in the case of the other antifungal agents. [19,20] All the experiments were performed in triplicate.

After reading the MIC, the minimum fungicidal concentration (MFC) was determined. A 100 μl aliquot from the wells in which no growth was observed was transferred to test tubes containing 2 ml of Sabouraud-dextrose broth (Difco, Detroit, MI, USA). A positive control (growth control) and a negative control (sterility control) were included in the test. The tubes were incubated for 7 days at 28°C and growth was observed visually. MFC was defined as the minimum concentration at which no fungal growth occurred. [21] These assays were performed in duplicate.

RESULTS

The *in vitro* sensitivity profile of nine commercially available antifungal agents against different species of dermatophytes isolated from patients with chronic renal failure was evaluated using the broth microdilution method. Of the azole antifungal agents, the best results in terms of MIC values were found with tioconazole, miconazole, itraconazole and ketoconazole (Table 1). Of these, the results obtained with tioconazole were significantly better, since this drug had the lowest geometric mean MIC. On the other hand, the activity of fluconazole was weak against all the species with the exception of *T. rubrum*; the remaining MIC values being high, particularly for samples of *M. gypseum* (Figure 1). Of the non-azole antifungal agents tested, terbinafine was found to be the most effective, followed by ciclopirox olamine.

DISCUSSION

Dermatophyte infections are probably the most common cutaneous fungal infections in humans and animals. [1] Over the past few decades, the number of antifungal agents used in clinical practice for the treatment of dermatophytoses has increased. [22] Nevertheless, not all species have the same susceptibility pattern and there is evidence that dermatophytes have become resistant to certain antimycotics. [16]

Although the precise cut-off points to determine the resistance of these fungi to the different antifungal agents are not known, in this study the parameters established in the Clinical and Laboratory Standards Institute (CLSI) M38-A document for filamentous fungi were taken into consideration, which establish MIC resistance ≥ 64 μg/ml for fluconazole and MIC ≥ 8 μg/ml for itraconazole and ketoconazole. [18]

Fluconazole (FCZ) was found to be the least active of all the antifungal agents evaluated (Figure 1) and this is in agreement with results published from other studies. [23,24] Furthermore, around 86% of *M. gypseum* isolates, 50% of *T. mentagrophytes* and 25% of *T. interdigitale* showed resistance to fluconazole, findings that are in agreement with the results published by Da Silva Barros and Hamdan. [23]

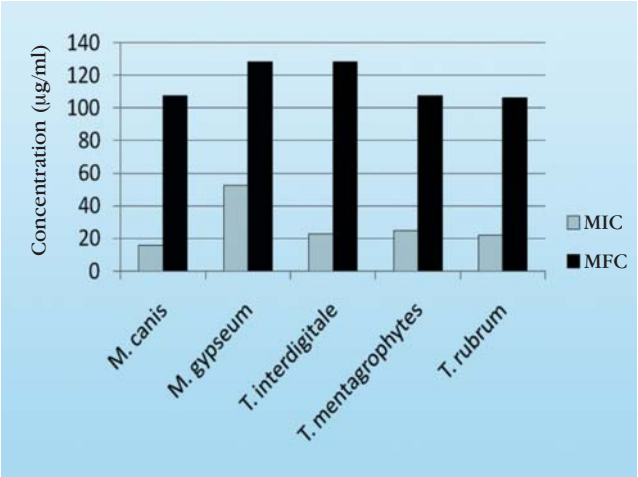
Nevertheless, *T. rubrum*, the species that is most often responsible for onychomycosis, with high recurrence rates, was more sensitive to fluconazole than the other species evaluated (Figure 1). The present results are in agreement with the findings of other investigators, who showed that the susceptibility to FCZ varies greatly from one species to another. [16,17,24]

Of the topical antifungal agents, ciclopirox olamine, miconazole, piroctone olamine and tioconazole, the best results were found with tioconazole, which had the lowest geometric mean MIC and MFC values for *M. gypseum*, *T. interdigitale* and *T. rubrum* (Figures 2, 3 and 4). These results show that the fungicidal effect of tioconazole is greater than that of miconazole, as shown in the study by Sobue and Sekiguchi. [25] The mean geometric MFC values of ketoconazole, fluconazole and itraconazole confirm that high concentrations of these medications are required to obtain their fungistatic effect, according to the mechanism of azoles. [26] Furthermore, these results

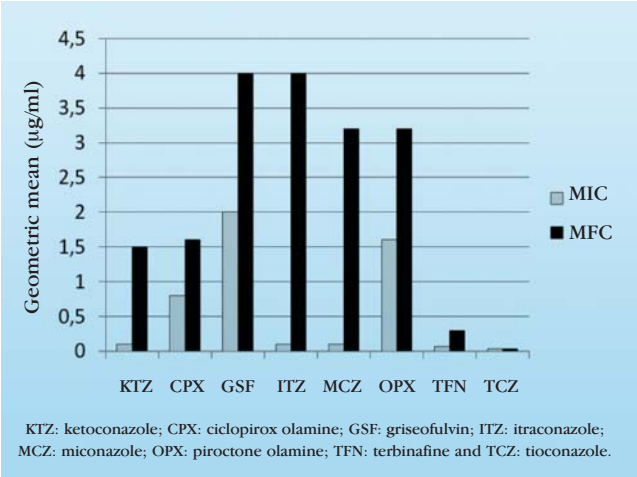
Table 1: *In vitro* susceptibility testing of five species of dermatophytes against nine commercially available antifungal agents

Isolates	Antifungal agents (μg/ml)																
	KTZa	CPXa		FCZa		GSFa	ITZa		MCZa		OPXa		TFNa		TCZa		
	MICb	MFCb	MICb	MFCb	MICb	MFCb	MICb	MFCb	MICb	MFCb	MICb	MFCb	MICb	MFCb	MICb	MFCb	MICb	FCb
M. canis																	
14	0.1	8	0.5	1	4	64	1	2	1	8	0.5	1	1	2	0.03	16	0.2	2
22	0.2	16	0.5	1	32	>128	0.2	2	0.06	>16	0.03	4	1	2	0.03	2	0.03	0.03
43979	0.2	16	1	1	16	128	2	2	0.5	1	0.2	1	2	2	0.03	0.03	0.2	4
48	0.5	8	1	1	32	>128	2	8	0.5	16	0.2	2	2	2	0.03	4	0.2	4
GMc	0.2	11.3	0.7	1	16	107.6	1	2.8	0.4	6.7	0.2	1.7	1.4	2	0.03	1.4	0.2	1
M. gypseum																	
18	1	>16	0.5	2	128	>128	2	2	0.2	>16	0.5	4	2	16	0.5	8	0.03	0.03
29	2	>16	1	4	128	>128	2	8	0.5	>16	1	16	2	>16	2	16	0.03	0.06
35	0.1	16	16	16	4	>128	2	2	0.1	2	0.2	4	1	2	0.03	2	0.03	0.03
43995	2	>16	4	2	64	>128	2	8	0.2	>16	1	16	2	>16	1	16	0.03	0.2
44000	0.5	>16	2	2	64	128	4	4	0.5	2	1	1	2	4	0.03	16	1	4
44704	1	16	0.5	2	64	>128	1	4	0.2	16	1	16	2	4	0.5	8	0.03	0.03
66	1	8	2	2	64	>128	2	4	0.5	8	0.5	2	4	8	0.03	2	0.5	8
GMc	0.8	14.5	1.8	3	52.5	128	2	4	0.3	8	0.6	5.4	2	7.2	0.2	7.2	0.07	0.2
T. interdigitale																	
45	0.06	4	0.5	2	4	>128	2	2	0.5	0.5	0.03	1	2	4	0.03	>16	0.03	0.05
72	0.1	4	1	2	32	>128	2	8	0.5	1	0.1	0.5	2	2	0.03	0.03	0.1	4
87	0.2	2	0.5	2	32	128	2	1	0.5	0.5	0.5	1	2	2	0.03	0.03	0.5	1
91	0.2	8	0.5	1	64	>128	4	>16	0.1	4	0.1	4	1	16	0.06	16	0.03	0.03
GMc	0.1	4	0.6	1.7	22.6	128	2.4	4	0.4	1	0.1	1.2	1.7	4	0.04	0.7	0.08	0.27
T. mentagrophythes																	
23	0.06	2	0.5	1	4	128	2	2	0.2	1	0.06	4	2	4	0.03	0.03	0.1	2
59	0.06	2	1	2	16	128	1	1	0.5	1	0.1	1	2	2	0.03	16	0.03	1
64	0.2	4	0.5	2	4	32	4	8	0.1	0.5	0.5	1	2	2	0.03	1	0.2	0.5
85	0.1	2	0.5	2	64	128	2	4	0.5	1	0.2	1	0.1	4	0.03	1	0.5	4
2996905	1	>16	2	8	64	>128	2	16	0.5	4	0.5	16	2	16	0.03	0.03	0.5	8
Santa Casa I	4	0.5	8	2	2	32	>128	4	16	0.5	8	1	8	1	8	0.03	0.03	0.5
Santa Casa II	8	1	8	2	4	64	>128	2	16	0.5	2	0.2	8	2	16	0.03	0.06	0.2
Santa Casa III	8	0.5	4	2	4	64	>128	2	4	0.5	16	0.5	2	0.5	4	0.2	>16	0.06
GMc	0.3	4.4	1	2.6	24.7	107.6	2.2	5.6	0.4	2.2	0.3	3.1	1.1	5.2	0.04	0.4	0.2	3.1
T. rubrum																	
1307	0.03	2	1	2	0.2	16	2	4	0.06	2	0.03	2	2	2	0.03	0.1	0.03	1
43316	0.03	0.1	0.5	1	4	64	1	1	0.1	2	0.03	2	2	2	0.03	0.03	0.03	1
43553	2	16	1	2	32	>128	4	>16	0.2	>16	1	8	1	8	0.5	8	0.03	0.03
GMc	0.1	1.5	0.8	1.6	2.9	50.8	2	4	0.1	4	0.1	3.2	1.6	3.2	0.07	0.3	0.03	0.3
Total	0.3	6.1	1.0	2.0	21.8	106.1	1.9	2.7	0.3	3.5	0.2	2.8	1.5	4.4	0.06	1.5	0.09	0.6
Range	0.03-2	0.1-16	0.5-16	1-16	0.2-128	16-128	0.2-4	1-16	0.06-1	0.5-16	0.03-1	0.5-16	0.1-4	2-16	0.03-2	0.03-16	0.03-1	0.03-8

aKTZ: ketoconazole; CPX: ciclopirox olamine; FCZ: fluconazole; GSF: griseofulvin; ITZ: itraconazole; MCZ: miconazole; OPX: piroctone olamine; TFN: terbinafine TCZ: tioconazole; b MIC: minimum inhibitory concentration; MFC: minimum fungicidal concentration; c GM: geometric mean.



Graph 1: Sensitivity profile of dermatophytes to fluconazole, based on the geometric mean minimum inhibitory concentration (MIC) and on the geometric mean minimum fungicidal concentration (MFC).



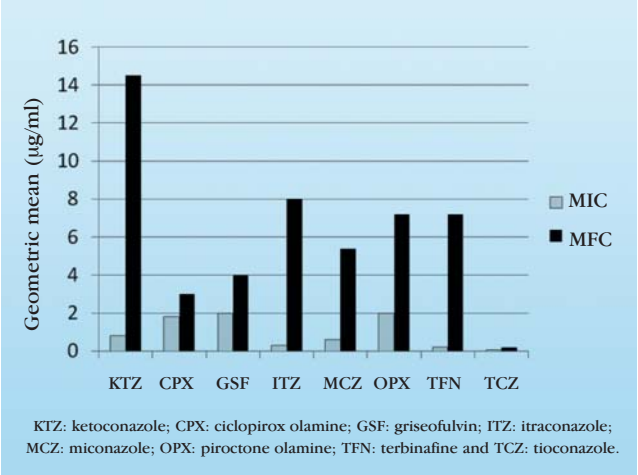
Graph 3: Sensitivity profile of *T. rubrum* to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole

highlight the problems involved in treating immunocompromised patients with this class of antifungal agents, since resistance to ketoconazole was 53.8%, resistance to fluconazole 100% and resistance to itraconazole 42.3%.

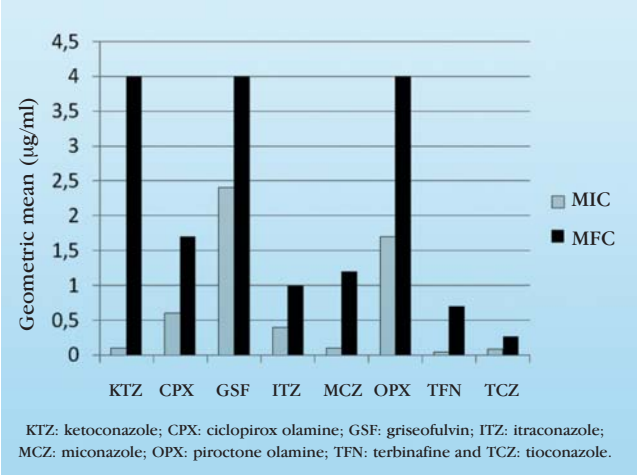
With respect to the other antifungal agents, it was impossible to determine the resistance rates, since standardization of the range of values corresponding to sensitivity or resistance has yet to be established. However, of the non-azole antifungal agents, terbinafine was found to be the most effective antimycotic agent (Figure 5). This finding is in agreement with the results reported by Favre et al. [21] Although less potent than terbinafine, ciclopirox olamine had better MIC and MFC values compared to griseofulvin and piroctone olamine for all the species evaluated (Figure 5). [20]

In general, the most effective antifungal agents were tioconazole against *M. gypseum* and *T. rubrum* (Figures 2 and 3) and terbinafine for the other species (Figures 4 and 6), including *M. canis* (Figure 7), which, according to the results reported by Clayton and Hay, shows poor sensitivity to azole antifungal agents. [27] Nevertheless, the sensitivity profile of some isolates was found to vary within the same species (Figure 8). This question reinforces the importance of analyzing sensitivity at least in all the fungal cultures obtained from patients with superficial mycoses in whom therapy has failed and, in view of their severity, in all cases of systemic mycoses. [17]

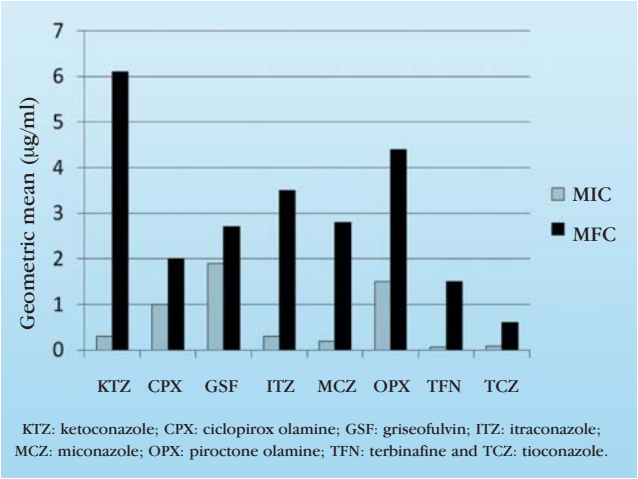
Therefore, knowing that fungal infections are naturally progressive and may advance to potentially severe stages in immunodepressed patients, identification of the species that is causing the infection in



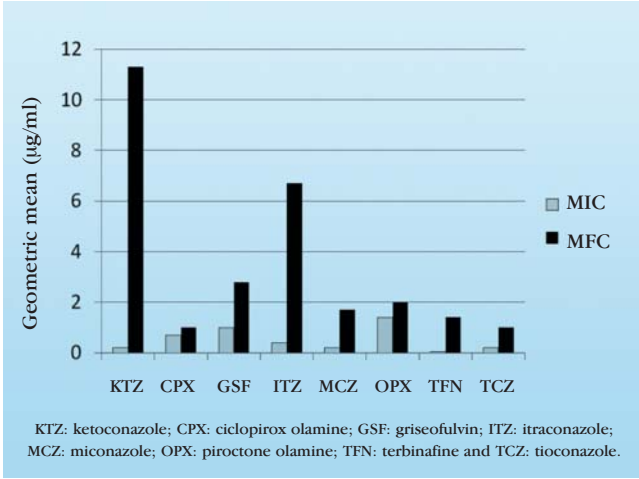
Graph 2: Sensitivity profile of *M. gypseum* to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole



Graph 4: Sensitivity profile of *T. interdigitale* to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole



Graph 5: Sensitivity profile of dermatophytes isolated from patients with chronic renal failure to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole

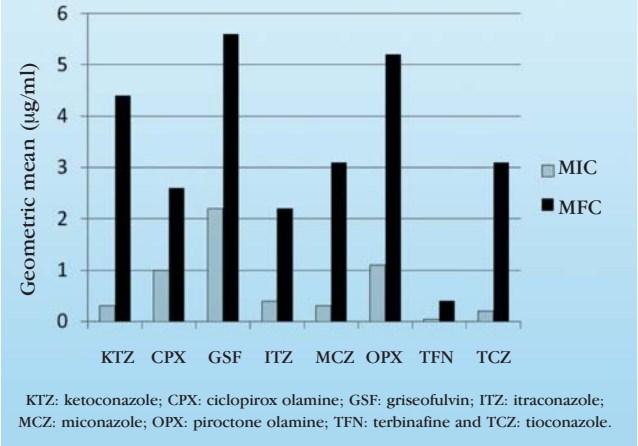


Graph 7: Sensitivity profile of *M. canis* to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole

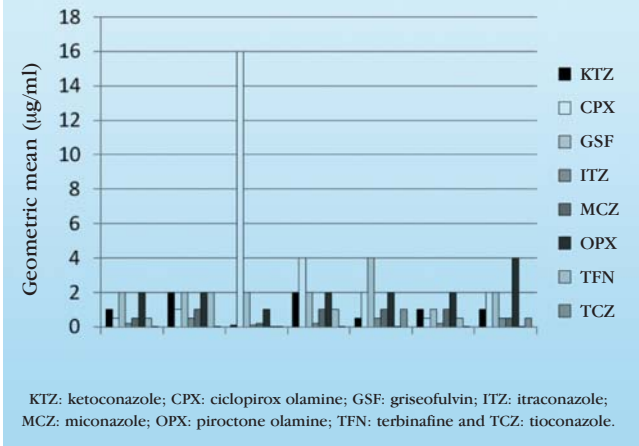
patients with dermatophytosis is fundamental in order to select the optimal treatment, since sensitivity to a single antimycotic agent may vary between species. [8] In patients with chronic renal failure undergoing hemodialysis, concern with the type of therapy and assurance of an effective medication is even greater given the high prevalence of dermatophytosis in these patients and the high rate of therapeutic failure. [7-9]

Oral treatment with antifungal agents such as terbinafine, itraconazole, ketoconazole and fluconazole represents the treatment of choice for dermatophytoses that fail to respond to topical medication. [16] Nevertheless, the use of these medications may result in undesirable side effects in the patient. Despite its low toxicity, terbinafine may cause secondary gastrointestinal and cutaneous side effects. [28] The use of azoles presents disadvantages such as hepatotoxicity and liver metabolism via cytochrome P450 (CYP), affecting the metabolism of other drugs. [9,26,28] These disadvantages for patients with chronic renal failure tend to be extremely compromising because of the defective renal function in these patients.

Therefore, considering the variation in the profile of activity of the different species of dermatophytes to the antifungal agents evaluated, identification of the species of the agent causing the infection is vital in order to plan treatment appropriately. This concern should be even greater in immunocompromised patients, since isolates of a single species may have different susceptibilities to the same antimycotic agent. For these patients in particular, *in vitro* evaluation of the antifungal activity of the drugs routinely indicated for the treatment of dermatophytoses may



Graph 6: Sensitivity profile of *T. mentagrophytes* to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole



Graph 8: Sensitivity profile of *M. gypseum* isolates to the antifungal agents: ketoconazole, ciclopirox olamine, griseofulvin, itraconazole, miconazole, piroctone olamine, terbinafine and tioconazole

help in selecting the type of therapy and the most appropriate drug, since the results of these studies are able to predict resistance or possible sensitivity of the microorganism.

Nonetheless, there are few reports on the correlation between antimicrobial activity *in vitro* and *in vivo*. It has to be taken into consideration that the response to antimicrobial therapy *in vivo* may be affected by several factors in the host, by the site and nature of the infection, by the pharmacokinetics of the antimicrobial agent, by protein binding and the drug's ability to penetrate infected areas. In certain cases, differences are also caused by variables related to the methodology of the *in vitro* susceptibility tests. [29,30] Therefore, it should be emphasized that the therapeutic success predicted *in vitro* may not occur *in vivo*.

CONCLUSION

In general, the sensitivity profile of the antifungal agents tested followed the same pattern as that found in previous studies, confirming the need to establish the species causing the dermatophytosis due to variations in the susceptibility profile from one species to another. Furthermore, the present results show the importance of performing sensitivity tests *in vitro*, since some isolates of the same species present different sensitivity profiles. ❑

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