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In vitro susceptibility of dermatophytes isolated from patients with end-stage renal disease: a case–control study

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Summary

Although the therapeutic efficacy of antifungals is well known for dermatophytosis in general population, limited data exist for patients with chronic kidney disease. The objectives of this study were to determine the dermatophyte species causing infection in patients with end-stage renal disease (ESRD) and *in vitro* susceptibility of isolated dermatophytes to antifungals. A total of 87 patients with ESRD who undergoing haemodialysis and 105 patients with normal renal function suspected with dermatophytosis were included. Skin scrapings or nail clippings were examined by direct microscopy and cultured on Sabouraud agar. *In vitro* antifungal susceptibility tests were performed using a broth microdilution method. Dermatophyte infections were identified in 32.2% of haemodialysis patients and in 29.5% of controls ($P > 0.05$). In both groups, *Trichophyton rubrum* was the most frequently isolated. Mean MIC values of the all studied antifungals for all of isolated dermatophyte strains from patients with ESRD were similar to those obtained in control group ($P > 0.05$). Terbinafine (TBF) had the lowest mean MIC values for all tested dermatophytes in both groups. We consider that TBF should be the treatment of choice for dermatophytosis in patients with chronic kidney disease, but the dose should be adjusted according to creatinine clearance and should be monitored for side effects.

Key words: Dermatophyte, chronic kidney disease, antifungals, *in vitro* susceptibility.

Introduction

Dermatophyte infections are common disorders worldwide and their incidence continues to increase.[1] Risk factors such as population migration, industrialisation, population ageing or increased incidence of diseases such as diabetes mellitus, malignancies, HIV infection, peripheral vascular diseases, or antibiotic and immunosuppressive therapies have influenced the epidemiological profile of dermatophyte infections. Some studies have shown that patients with chronic kidney disease (CKD) are more susceptible to dermatophytosis.[2–6] Although the therapeutic efficacy of terbinafine (TBF), itraconazole (ITZ), voriconazole (VCZ), fluconazole (FLZ) and ketoconazole (KTZ) is well known for dermatophytosis in general population, limited data exist with regard to patients with end-stage renal disease (ESRD).

In this case–control study we aimed to determine the spectrum of dermatophyte species causing infection in patients with ESRD (stage 5 CKD) and also to determine *in vitro* susceptibility of isolated dermatophytes in this patient group to KTZ, ITZ, VCZ, FLZ and TBF. We compared the findings with those in individuals with normal renal function.

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Materials and methods

Study population

A prospective, longitudinal, observational study with informed consent of patients was conducted. In this study, 87 patients (42 women and 45 men, sex ratio

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M/F 1.07) diagnosed with ESRD who undergoing haemodialysis and who were consulted for dermatophyte infections in the ambulatory of dermatology or were hospitalised in the Clinical County Emergency Hospital of Brasov were included. The average age of this group was 59.96 ± 10.10 years, with a range between 34 and 76 years. The average duration of the evolution of CKD at time of diagnosis was 7.35 ± 4.46 years, and the mean duration of performing haemodialysis was 2.72 ± 4.95 years. In parallel a control group consisting of 105 immunocompetent patients with normal renal function (59 men and 46 women) aged between 18 and 71 years (average age 54.59 ± 11.2 years) who showed signs of dermatophyte infections was also analysed. Pathological material was collected by scraping the skin or clipping the nail lesions from each patient from both groups. Skin and nail specimens were collected in Petri dishes and the samples were immediately transported to the mycology laboratory.

Isolation and identification of dermatophytes

The samples taken from infected areas were examined by direct microscopy. Only direct microscopy-positive specimens were cultured on Sabouraud dextrose agar medium with addition of cycloheximide, chloramphenicol and gentamicin (Bio-Rad, Marnes-la-Coquette, France) and incubated at 30 °C for 2–4 weeks. Dermatophyte species identification was based on macroscopic and microscopic characteristics of colonies grown on the culture medium.

In vitro susceptibility testing

Method

Antifungal susceptibility tests were performed using a broth microdilution method according to the criteria of Clinical and Laboratory Standards Institute (CLSI) M38-P[7] for filamentous fungi.

Antifungal agents

For testing *in vitro* susceptibility of dermatophytes, five antifungal substances were used: KTZ (Janssen Research Foundation, Beerse, Belgium), ITZ (Janssen Research Foundation, Beerse, Belgium), FLZ (Pfizer Inc., New York, NY, USA), VCZ (Pfizer Inc., New York, NY, USA) and TBF (Novartis, Basel, Switzerland). ITZ, KTZ, FLZ and VCZ were prepared in 100% dimethyl sulfoxide solution, and TBF was dissolved in dimethyl sulfoxide solution with 5% Tween 80 following the protocol of Jessup.[8]

Dilutions

Ten-serial twofold dilutions to reduction of 100 times of the initial concentration were performed for each antifungals. Concentrations of serial drug dilutions ranged 0.0625–32 μg/ml for KTZ and ITZ, 0.125–64 μg ml^{-1} for FLZ and 0.0078–4 μg ml^{-1} for VCZ and TBF.

Inoculum preparation

Obtained colonies of dermatophytes were recultured on Sabouraud agar medium at 30 °C for 7–15 days, time necessary to obtain sporulation. The Petri plates with Sabouraud agar medium were covered with sterile normal saline (0.9%), then dermatophyte colonies were gently scraped with a sterile loop and suspension consisting of fragments of hyphae and conidia was transferred to a sterile tube with a Pasteur pipette. The tube was left at room temperature for 15–20 min for sedimentation of heavy particles, then the upper suspension was centrifuged at 400 ***g*** for 15 s. The supernatant was further diluted to 1 : 50 in buffered RPMI 1640 and standardised spectrophotometrically to approximately 0.5 McFarland units at a wavelength of 520 nm and a transmission of 70–80% to the desired concentration of 0.5–5 × 10^4 colony-forming units (CFU) per ml for final test inoculums.

Medium

RPMI 1640 medium (Sigma-Aldrich, Bucharest, Romania), which was buffered at pH 7.0 with 0.165 mol l^{-1} 3-(N-morpholino) propanesulphonic acid (MOPS), was used for antifungal sensitivity tests. The tests were performed in sterile, round-bottomed, 96 U-shaped well microplates, each well having a nominal capacity of 300 μl. Aliquots of 100 μl of the serial twofold dilutions of the antifungal drugs and then 100 μl of the diluted inoculums suspensions were added into each well in columns 2–11. Wells of the first column were filled with 200 μl of RPMI 1640 medium and served as sterility control. A quantity of 100 μl of inoculum solution and 100 μl of RPMI 1640 medium were distributed in the 12th column's wells serving as growth control. *Candida parapsilosis* (ATCC 22019), *Candida krusei* (ATCC 6258), *Trichophyton rubrum* (ATCC MYA-4438) and *T. mentagrophytes* (ATCC MYA-4439) were included as quality control.

Incubation time and temperature

Microdilution plates were incubated at 30 °C for 7 days. Rate of growth in each well was visually assessed daily based on comparison with growth in

wells containing only antimycotic substance and those drug free, starting 48 h after inoculation.

Statistical analysis

Mean minimum inhibitory concentration (MIC), MIC_{50} and MIC_{90} of each antifungal drug for each dermatophyte species isolated among control group subjects and in haemodialysis patients group were determined. In accordance with the broth microdilution method proposed in M38-P protocol,[7] the MIC was defined as the lowest concentration showing 80% growth inhibition for azoles, and 100% for TBF comparing with the growth of the drug-free control.[9,10] A dermatophyte species was considered resistant to an antifungal agent when MIC was ≥ 8 μg ml^{-1} for KTZ, ≥ 4 μg ml^{-1} for ITZ, VCZ and TBF and ≥ 64 μg ml^{-1} for FLZ, according to the criteria of CLSI *M38-P*.[7] Statistical differences in the frequency patterns of dermatophyte species between patients with ESRD and control group were assessed using Fisher's exact chi-square test. The significance of difference between mean values of MICs of the five antifungal substances tested in the above-mentioned groups was calculated using the Student's *t*-test. Values of *P* less than 0.05 were considered significant.

Results

After mycological investigations among the 87 haemodialysis patients, positive samples for dermatophytes resulted in 28 patients (32.2%), for *Candida spp*. in nine (10.3%) and for *Scopulariopsis brevicaulis* in one case (1.2%). Frequency of dermatophyte infections according to aetiology of ESRD is shown in Table 1. Tinea unguium was the most frequent clinical form of dermatophytosis encountered in 13 of the 28 patients (46.4%) with ESRD and dermatophyte infection, followed by tinea pedis in nine patients (32.1%), tinea cruris in three patients (10.7%), tinea manum in two patients (7.1%) and tinea corporis in one patient (3.6%). Duration of evolution of ESRD and duration of performing haemodialysis did not represent risk factors for dermatophyte infection ($P > 0.05$).

Table 1 Frequency of the dermatophyte infections depending on the aetiology of ESRD

		Dermatophyte infections	
Aetiology of ESRD	No. of patients	No. of patients	%
Diabetes mellitus	44	15	34.1
Nephrotic syndrome	5	2	40.0
Systemic lupus erythematosus	5	2	40.0
Systemic sclerosis	3	1	33.3
Polycystic kidney disease	6	2	33.3
Arterial hypertension	14	4	28.6
Unspecified glomerulonephritis	9	2	22.2
Systemic vasculitis	1	0	0
Total	87	28	32.2

ESRD, end-stage renal disease.

Dermatophyte and candidal infection rates in control group were 29.52% (31 patients) and 8.57% (9 patients) respectively. Tinea unguium was also the most frequent clinical form of dermatophytosis in control group being found in 13 cases (41.9%), followed by tinea pedis in 10 patients (32.3%), tinea cruris in four patients (12.9%), tinea corporis in two patients (6.4%) and tinea manum and tinea faciei in one patient each (3.2%).

Aetiological agents for each clinical form of dermatophytosis in the two groups of patients are presented in Table 2. In both groups, *T. rubrum* was the most frequently isolated. There was no statistically significant difference in the frequency patterns of *T. rubrum, T. mentagrophytes, M. canis* and *E. floccosum* between the two groups ($P > 0.05$).

The MIC statistics including mean MIC, MIC_{50} and MIC_{90} values of KTZ, ITZ, VCZ, FLZ and TBF for *T. rubrum, T. mentagrophytes, M. canis* and *E. floccosum* in patients with ESRD and in control group are summarised in Table 3. Mean MIC values of the all studied antifungals for all of isolated dermatophyte strains from patients with ESRD were similar to those obtained in control group ($P > 0.05$). *In vitro* activity of KTZ, ITZ, VCZ, FLZ and TBF against dermatophytes in patients with ESRD was similar to that of immunocompetent patients with normal renal function. TBF had the lowest and FLZ had the highest mean MIC, MIC_{50} and MIC_{90} values for all tested dermatophytes in both groups. No case of resistance to any of the five tested antifungals was recorded.

Discussion

Studies have shown that patients with CKD are more susceptible to dermatophyte infections, mainly to onychomycosis, that is the second most common nail disease in patients on haemodialysis with a prevalence ranging from 6.2% to 69.8%.[2–6] In patients with advanced CKD, increased susceptibility to skin infections seems to be caused by immunological and histological skin changes induced by uraemia.[11–13]

In this study, we noticed the existence of a higher frequency of the dermatophyte infections in patients

Table 2 Aetiological agents and clinical forms of dermatophyte infections in both groups

	T. rubrum		*T. mentagrophytes*		*M. canis*		*E. floccosum*	
	ESRD	Control	ESRD	Control	ESRD	Control	ESRD	Control
Tinea unguium	11	12	2	1	–	–	–	–
Tinea pedis	7	8	2	2	–	–	–	–
Tinea cruris	2	2	–	1	–	–	1	1
Tinea corporis	–	–	–	–	1	2	–	–
Tinea manum	2	1	–	–	–	–	–	–
Tinea faciei	–	–	–	–	–	1	–	–
Total strains (%)	22 (78.6)	23 (74.2)	4 (14.3)	4 (12.9)	1 (3.6)	3 (9.7)	1 (3.6)	1 (3.2)

ESRD, end-stage renal disease.

with ESRD undergoing haemodialysis compared with controls ($P > 0.05$). Our findings indicate that, similar to the immunocompetent population, *T. rubrum* is the principal responsible agent for dermatophyte infection in patients with ESRD, being followed by *T. mentagrophytes*. Yeast and moulds infections were diagnosed in 10.34% and 1.15% of haemodialysis patients respectively. Unlike other previous studies,[2,14,15] there was no statistical correlation between dermatophyte infection frequency and duration of evolution of ESRD or duration of performing haemodialysis ($P > 0.05$).

Oral antifungal therapy represents the treatment of choice for dermatophytoses.[16] The main goal in treating haemodialysis patients is choosing the most effective antifungal drug. Nevertheless, the use of these medications may result in undesirable side effects that in patients with ESRD could be particularly dangerous. Although the clinical studies in immunocompetent individuals reveal that TBF has higher cure and slower relapse rates with shorter treatment duration,[17] less clinical data are available about its efficacy in patients with ESRD. We found that all the five tested antifungal drugs are effective against *T. rubrum, T. mentagrophytes, M. canis* and *E. floccosum* in haemodialysis patients, but TBF has the higher antidermatophyte activity, the mean MIC of TBF being much lower than

Table 3 Mean MIC values of antifungals for all of the isolated dermatophyte species in both groups

		Mean MIC		MIC_{50}		MIC_{90}	
Antifungal	Dermatophyte species	ESRD ($\mu g\ ml^{-1}$)	Control ($\mu g\ ml^{-1}$)	ESRD ($\mu g\ ml^{-1}$)	Control ($\mu g\ ml^{-1}$)	ESRD ($\mu g\ ml^{-1}$)	Control ($\mu g\ ml^{-1}$)
Ketoconazole	*T. rubrum*	0.18	0.172	0.15	0.062	2	1
	T. mentagrophytes	1.125	0.56	1	0.25	2	1
	M. canis	0.5	0.66	0.5	0.5	0.5	1
	E. floccosum	0.5	0.25	0.5	0.25	0.5	0.25
Itraconazole	*T. rubrum*	0.11	0.08	0.062	0.062	0.5	0.5
	T. mentagrophytes	0.093	0.078	0.125	0.062	0.125	0.25
	M. canis	0.25	0.208	0.25	0.062	0.25	0.25
	E. floccosum	0.125	0.0625	0.125	0.0625	0.125	0.0625
Fluconazole	*T. rubrum*	5.9	6.6	4	4	8	8
	T. mentagrophytes	12	9	8	8	16	32
	M. canis	16	9.3	16	8	16	16
	E. floccosum	4	2	4	2	4	2
Voriconazole	*T. rubrum*	0.14	0.11	0.062	0.062	0.5	0.25
	T. mentagrophytes	0.087	0.062	0.0625	0.125	0.125	0.5
	M. canis	0.25	0.145	0.25	0.031	0.25	0.5
	E. floccosum	0.125	0.0625	0.125	0.0625	0.125	0.0625
Terbinafine	*T. rubrum*	0.008	0.008	0.007	0.007	0.015	0.015
	T. mentagrophytes	0.017	0.011	0.015	0.015	0.031	0.030
	M. canis	0.031	0.041	0.031	0.015	0.031	0.062
	E. floccosum	0.007	0.007	0.007	0.007	0.007	0.007

ESRD, end-stage renal disease; MIC, minimum inhibitory concentration; MIC^{50}, minimum inhibitory concentration at which 50% of the isolates inhibited; MIC^{90}, minimum inhibitory concentration at which 90% of the isolates inhibited.

Table 4 Antifungal agents: dosing requirements in patients with chronic kidney disease[23,25,27–29]

		Dosage adjustment (percentage of usual dose) based on GFR (ml min^{-1} per 1.73 m^2)		
Antifungals	Usual dosage	>50%	10–50%	<10
Ketoconazole	200–400 mg po every 24 h	100	100	100
Fluconazole	100–400 mg po every 24 h	100	50	50
Itraconazole	100–200 mg po every 12 h	100	100	50 (avoid IV form in CrCl <30 ml min^{-1} due to decreased clearance of vehicle injectable product)
Voriconazole	200–400 mg po or 4-6 mg kg^{-1} IV every 12 h	100	100 (avoid IV form in CrCl <50 ml min^{-1} due to decreased clearance of vehicle injectable product)	100 (avoid IV form in CrCl <50 ml min^{-1} due to decreased clearance of vehicle injectable product)
Terbinafine	250 mg po every 24 h	100	50	Avoid use (insufficient pharmacokinetic data)

GFR, glomerular filtration rate; CrCl, creatinine clearance; IV, intravenous; po, per os.

the other antifungal agents, and FLZ was the least effective antifungal drug. The study results of Magagnin *et al.* [18] emphasise the issues involving therapy with azole antifungals in patients with CKD considering that FLZ resistance rate was 100%, and 53.8% to KTZ and 42.3% to ITZ. In contrast, non-azole antifungals, as TBF, have a much higher antidermatophyte activity.[19]

The use of antifungal agents in patients with ESRD requires careful consideration of not only the degree of renal insufficiency but also the dermatophyte strain and the antifungal pharmacokinetic. Only few antifungal agents (FLZ and flucytosine) are renally eliminated as unchanged drug or active metabolite.[20] In fact, of all the available systemic antidermatophyte agents, only FLZ and TBF require dosing modification when given to patients with decreased levels of creatinine clearance (Table 4).[21] Dosage reduction of FLZ is mandatory in patients with renal impairment. In patients whose creatinine clearance is between 10 and 60 ml min^{-1}, it is recommended to reduce FLZ doses by 50%, by halving the dose or by doubling the dosing interval.[22,23] Little information is available regarding the handling of TBF in renal failure, but the clearance of TBF is decreased by approximately 50% if GFR<50 mL/min. Approximately 70% of the administered dose of TBF is eliminated in the urine. Patients with impaired renal function (CrCl < 50 ml min^{-1}) should receive half of the normal dose. There is no experience of the use of TBF in patients with creatinine clearance values less than 20 ml min^{-1}.[24] Dose adjustment is not required for oral administration of KTZ, ITZ and VCZ in patients who have renal insufficiency.[25–28] A particular danger is represented by the formulations containing cyclodextrins, which are present in the intravenous preparations of ITZ and VCZ and can accumulate in CKD. Therefore, the use of these formulations in patients with creatinine clearance <50 ml min^{-1}, in the case of VCZ, and 30 ml min^{-1}, in the case of ITZ, is cautioned for these formulations.[27–29]

As TBF was the most active antidermatophyte agent *in vitro* and, considering that its antidermatophyte activity compared with azoles and that its drug interactions are not typically an issue, we consider that TBF should be the treatment of choice for dermatophytosis in patients with CKD, but the dose should be adjusted according to creatinine clearance and should be monitored for side effects. However, further large studies are required to evaluate the safety of antifungals administration in patients with renal failure.

Conflict of interest

The authors have no conflict of interest to declare.

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