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Contact allergy to antifungals: results of a 12-year retrospective study

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Abstract:

Background: Contact allergy has been reported as a side effect of topical antifungals, although most evidence has come from small case series.

Objective: Investigate the frequency and associated factors of contact allergy to topical antifungals.

Methods: We performed a retrospective analysis of the data of the Contact Allergy Unit of a University Dermatology Department, between January 2009 and April 2021. From a cohort of 3788 patients tested in our unit, aimed testing was performed in 482 patients using topical antifungals (Chemotechnique Diagnostic, Vellinge Sweden or AllergEAZE) and, in some cases, commercial preparations “as is”.

Results: Contact allergy to antifungals was found in 27 patients (0.71% of consecutively tested patients and 5.6% of those who had aimed testing). Foot and leg eczema were the clinical presentation in 12 (44.4%) and 10 (37.0%) patients, respectively. Positive reactions were observed mostly with econazole nitrate 1% alc. (51.9%), miconazole 1% alc. (48.9%), tioconazole 28% solution (40.7%) and clotrimazole 5% pet. (18.5%). Fifteen patients (55.6%) presented sensitization to more than one antifungal.

Conclusions: Although contact allergy to antifungals was uncommon and occurred mostly associated with foot dermatitis. Most patients were sensitized to more than one chemical, particularly to azoles, which may limit future choices of topical antifungal treatment.

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1. Background: Topical antifungals (TAF) are commonly used in the treatment of superficial dermatophyte and yeast infections of the skin, nails and hair. Allergic contact dermatitis has been reported as a side effect of these medications, although most evidence has come from small case series.¹⁻⁴ The aim of this study was to investigate the frequency and associated factors of contact allergy to topical antifungals.

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2. Methods: We performed a retrospective analysis of the data of the Contact Allergy Unit of Coimbra University Dermatology Department, between January 2009 and April 2021. Aimed testing with TAF was performed in patients who reported dermatitis possibly induced or aggravated by topical antifungals, and econazole and miconazole were tested in patients with foot dermatitis as part of the shoe/foot series. We used allergens from Chemotechnique Diagnostic (Vellinge Sweden), AllergEAZE, pure chemicals kindly supplied by the pharmaceutical industry and prepared in house and commercial preparations of topical antifungals “as is” (Table 1). TAF allergens were applied in Finn chambers on Scanpor Epitest Ltd Oy (Tuusula, Finland) and in the more recent years in IQ-Ultra (Chemotechnique diagnostics). On day (D) 2, patches were removed, and reading was done on D2 and D4/D5 (2009 to 2018) or D3 and D7 (2019 to 2021). Patch test reactions were scored as ‘+’, ‘++’ or ‘+++’, according to ESCD recommendations.⁵ Data collected from patient’s files included the gender, age, suspicion of an occupational cause, atopic comorbidities and presence of eczema of the hand, face, leg or foot. Positive reactions were recorded in the Unit database. Informed consent was obtained from each patient. Statistical analysis was performed in SPSS Statistics v22.0 (SPSS Inc., IBM-SPSS, Chicago).

3. Results: From a cohort of 3788 patients (2720 F/ 1068 M) tested in our unit during this period, aimed testing was performed in 482 patients (69.1% females, 70.5% aged > 40 years and 35.8% with lesions localized to the leg and/or feet) (Table 1).

Contact allergy to antifungals was found in 27 patients (0.71% of all patients tested and 5.6% of those who had aimed testing) with a mean age of 55.8 ± 19.0 years and 63% (n=17) females. Foot and leg eczema were the clinical presentation in 12 (44.4%) and 10 (37.0%) patients, respectively, with overrepresentation of this localization in comparison with the aimed tested sample. However, we only found a significant difference in the group with foot eczema ($p < 0.01$). Eczema of the face (14.8%) and hand (18.5%) were less common and not significantly different from the aimed group tested, as well as atopy (14.8%) (Table 1).

Positive reactions were mostly observed with econazole nitrate 1% alc. (51.9%), miconazole 1% alc. (48.9%), tioconazole 1% pet. (22.2%), clotrimazole 5% pet. (18.5%) and tioconazole 28% solution nail solution (Trosyd®) (18.5%). Reactivity to isoconazole 2% pet, sertaconazole 2% cream, ketoconazole 2% pet., terbinafine 1% cream, ciclopirox 8% nail lacquer and bifonazole 1% cream were observed in less than 10% (Table 2).

Fifteen patients (55.6%) presented sensitization to more than one antifungal (Fig. 2), with 9 (33.3%), 3 (11.1%), 1 (3.7%) and 2 (7.4%) patients being simultaneously sensitized to 2, 3, 4 and 5 antifungals, respectively, mostly among azole antifungals (Table 3). Miconazole (73.3%), econazole (60%) and tioconazole (60%) reactivities were present in the majority of these patients.

Reactions were considered relevant in 12 patients (44.4%), particularly in 5 cases related with the use of a 28% tioconazole nail solution which caused periungual and foot dermatitis in most cases, with ectopic lesions in the leg (Fig. 1). In further 10 patients (37.0%) the TAF possibly contributed to the dermatitis and in the remaining 5 patients the reactions were considered not relevant.

4. Discussion: Fungal skin infections have been placed as the 5th skin disease with the highest years lived with disability (YLD) score, of the Global Burden of Disease.⁶ Topical antifungals (TAF) constitute a commonly prescribed topical therapy.^{7,8} In an Australian study with residents of aged care facilities, TAF were the most common prescribed topical antimicrobials, with clotrimazole (83.5%) and miconazole (9.1%) being the most frequent choices.⁸ The authors reported that TAF were commonly prescribed for as needed administration (38.8%) and for periods greater than 6 months (11.3%).⁸ These prolonged and, sometimes, unnecessary administration may predispose to sensitization to TAF. In fact, the frequency of positive patch tests reactions to TAF is strongly influenced by local prescribing habits, availability in the country and also by the drug concentration on topical formulations.¹

Contact allergy to TAF has been mainly reported by case reports or small case series of individual antifungals,^{2,3,9} and there is lack of information regarding the prevalence of TAF contact allergy. A multicenter study from the German Contact Dermatitis Research Group and the Information Network of Departments of Dermatology between 2001 and 2002 found positive reactions to topical antifungals only in 12 out of 1254 patients (0.94%),¹⁰ in a percentage that is not very different from ours. Ciclopiroxolamine tested at 1% pet. had the highest number of positive and doubtful reactions, with no reactions to other TAF. This contrasts with our study where we found frequent cross-reactivity between imidazoles. This has been previously demonstrated, although seldom,^{1,11,12} namely between miconazole, econazole and isoconazole, between sulconazole, miconazole and econazole, between isoconazole and tioconazole,^{1,4} between tioconazole, econazole and miconazole, between ticonazole, econazole and isoconazole,⁴ and also between sertaconazole and miconazole.¹² Furthermore, the multiple positive reactions observed in our study can be explained by concomitant exposure to different TAF.

Most cases occurred associated with foot dermatitis, related either with the use of nail solutions with high antifungal concentrations for the treatment of onychomycosis or with TAF used in foot dermatitis, namely *Tinea pedis*. As this is a frequent and recurrent condition and antifungals are often used in the feet, where sweating, occlusion and previous inflammation may favour sensitization, it might be adequate to include one or two antifungals in a shoe/foot series to avoid missing this possible cause of foot dermatitis.

5. Conclusions: Our findings suggest that contact allergy to antifungals is uncommon. Interestingly, when imidazoles are involved, more than half of the patients show sensitization to more than one chemical, which may limit future choices of antifungal treatment and justify patch testing with an extended TAF series.

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Table 1 – Clinical characteristics of all patients tested, those with aimed patch testing with topical antifungals and positive reactions, comparing the population with no reactions with those with positive reactions.

Characteristic	Whole population (3788) N (%)	Patients tested with topical antifungals, n (%)	Patients with positive reactions to topical antifungals, n (%)	P-value
Male	1000 (26.4%)	149 (30.9)	10 (37.0)	0.48
Age ≥ 40 years	1962 (51.8%)	340 (70.5)	21 (77.8)	0.40
Atopy	886 (23.4%)	69 (14.3)	4 (14.8)	0.94
Occupational cause	640 (16.9%)	52 (10.8)	3 (11.1)	0.96
Hand eczema	1018 (26.9%)	84 (17.4)	5 (18.5)	0.88
Face eczema	1026 (27.1%)	96 (19.9)	4 (14.8)	0.49
Leg eczema	231(6.1%)	113 (23.4)	10 (37.0)	0.09
Foot eczema		60 (12.4)	12 (44.4)	<0.01

Table 2 – Discrimination of positive patch test reactions to topical antifungals. [†]Chemotechnique diagnostics. [‡]AllergEAZE. [§]Pure product kindly supplied by the pharmaceutical industry and prepared in house.

Allergen	Number of patients tested	Positive patch tests, n (%)	Relevant, n/ Possibly relevant, n
econazole nitrate 1% alc. [†]	482	14 (51.9)	4 / 5
miconazole 1% alc. [†]	482	13 (48.9)	5 / 5
clotrimazole – 1 or 5% pet. [‡]	305	5 (18.5)	4 / 0
tioconazole – 1% pet. [†]	145	6 (22.2)	6 / 0
terbinafine 1% cream	131	2 (7.4)	2 / 0
ketoconazole 2% pet. [§]	129	0	0
isoconazole 2% pet. [§]	129	2 (7.4)	2 / 0
sertaconazole 2% cream	129	2 (7.4)	2 / 0
bifonazole 1% cream “as is”	129	1 (3.7)	1 / 0
tioconazole 28% solution Trosyd® nail solution “as is”	17	5 (18.5)	5 / 0
ciclopirox 8% nail lacquer	12	2 (7.4)	0 / 1

Table 3 - Discrimination of the positive reactions among patients with reactions to two or more topical antifungals. Patch test reactions were scored as ‘-’, ‘+’, ‘++’ or ‘+++’, according to ESCD recommendations.⁵ [†]Including both reactions to tioconazole 1% pet. and tioconazole 28% nail solution.. n.t., not tested.

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Total, N (%)
Bifonazole	-	-	-	-	-	n.t.	-	-	-	-	n.t.	n.t.	n.t.	n.t.	-	1 (6.7)
Clotrimazole	-	+	-	++	++	-	+	-	-	-	-	-	-	-	-	4 (26.7)
Econazole	+++	++	+	+	-	-	+	-	+	-	+	++	-	-	++	9 (60.0)
Isoconazole	-	-	-	-	-	n.t.	+	-	-	-	n.t.	n.t.	n.t.	n.t.	-	2 (13.3)
Miconazole	+++	++	++	+	-	-	+	-	+	+	+	+	-	++	++	11 (73.3)
Sertaconazole	-	+++	-	-	-	-	-	-	-	-	+	n.t.	-	-	-	2 (13.3)
Terbinafine	-	-	-	-	-	-	-	-	-	-	-	-	++	-	-	1 (6.7)
Tioconazole [†]	-	+	+	-	++	+	+	+++	-	+	-	-	+++	++	-	9 (60.0)
Ciclopirox	-	-	-	-	-	+	-	+	-	-	-	-	-	-	-	2 (13.3)

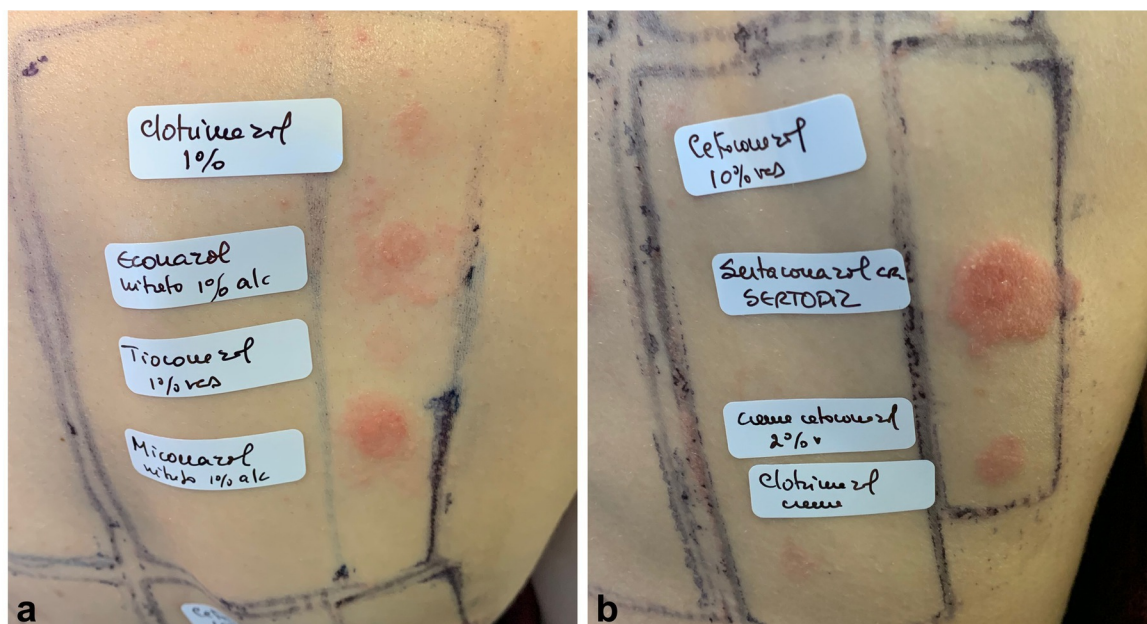
Legends:

Figure 1 – Patient with bilateral foot eczema affecting the periungual region, with ectopic eczema lesions in the legs. This patient presented reactivity to 28% tioconazole nail solution.

Figure 2 – Patch tests confirming reactivities to multiple topical antifungals in the same patient.



COD_14076_Figure 1.jpg



COD_14076_Figure 2.jpg