Our Dermatology Online

Review Article

Recurrent pityriasis versicolor: A short review of clinical features and antifungal and non-antifungal treatment options

Andrés Tirado-Sánchez[1,2], Mariana G. Ungson-García[3], Mariel Isa-Pimentel[4], Leonel Fierro-Arias[1], Sofía Beutelspacher[1], Sandra Miranda-Mauricio[5], Alexandro Bonifaz[1]

[1]Dermatology Department, Hospital General de México, México city, Mexico, [2]Internal Medicine Department, Hospital General de Zona 30, Instituto Mexicano del Seguro Social, México City, Mexico, [3]Dermatology Service, Hospital Reginaol "Dr Valentín Gómez Farias" ISSSTE, Zapopan, Jalisco, Mexico, [4]Instituto Dominicado de Dermatología y Cirugía de Piel "Dr Huberto Bougart. Santo Domingo, Dominican Republic, [5]Central Laboratory, Hospital Adolfo López Mateso. ISSSTESON, Cd. Obregón, Sonora, Mexico

Corresponding author: Prof. Alexandro Bonifaz, MD PhD, E-mail: a_bonifaz@yahoo.com.mx

ABSTRACT

Objective: We conducted a systematic review of the literature from the PubMed database from January 1, 2010, to December 31, 2021. The search criteria were "(pityriasis versicolor OR tinea versicolor) AND treatment," with the full text available and the English language required. This review focuses on the clinical evidence supporting the efficacy of antifungal and non-antifungal treatment for pityriasis versicolor. **Background:** Pityriasis versicolor is a chronic superficial mycosis caused by the *Malassezia* species. The condition is one of the most common infections worldwide, particularly in tropical climates. Although it is a superficial infection, recurrences are high due to the presence of *Malassezia* in the normal skin flora. **Summary:** Topical and oral antifungal treatments effectively reduce the recurrence, leading to a lasting clinical and mycological cure. In addition to antifungal therapies, non-antifungal treatments have shown efficacy in cases of recurrent pityriasis versicolor and could be used as maintenance or preventive therapy. Due to high recurrence rates, prophylactic treatment may be necessary.

Key words: Pityriasis versicolor, Superficial mycosis, Tinea versicolor, Treatment

INTRODUCTION

Pityriasis versicolor (PV) is a superficial chronic fungal infection caused by yeasts of the *Malassezia spp.* genus [1,2]. These species are commensals on human skin and warm-blooded animals, such as pigs, monkeys, goats, horses, dogs, cats, and others, developing skin diseases and systemic infections in humans and animals [3].

Malassezia yeasts have been classified into at least fourteen species; eight have been isolated from human skin. The frequency varies depending on country; *M. furfur* is the main species in Indonesia and Brazil, *M. sympodialis* in Canada, and *M. sympodialis* and *M. globosa* in Argentina. The isolation of *M. slooffiae* and *M. restricta* is less frequent [1].

M. sympodialis is the predominant species in human skin, healthy or diseased, and is usually found on the trunk, while *M. globosa* is found in PV scales and healthy skin and *M. restricta* seems to be associated with pityriasis capitis [4]. *M. pachydermatis*, an agent of external otitis in cats and dogs, has also been considered responsible for some cases of systemic infection, mainly in premature children [1].

Malassezia-related skin diseases include head and neck dermatitis, seborrheic dermatitis, PV, and *Malassezia*

How to cite this article: Tirado-Sánchez A, Ungson-García MG, Isa-Pimentel M, Fierro-Arias L, Beutelspacher S, Miranda-Mauricio S, Bonifaz A. Recurrent pityriasis versicolor: A short review of clinical features and antifungal and non-antifungal treatment options. Our Dermatol Online. 2023;14(4):436-447.

Submission: 24.04.2023; **Acceptance:** 13.06.2023
DOI: 10.7241/ourd.20234.22

folliculitis [5]. *M. japonica*, a recently described species was isolated mainly in the Japanese and Chinese populations with psoriasis, atopic dermatitis, seborrheic dermatitis, and healthy individuals [6]. Romero-Sandoval et al. [7] reported the isolation of *M. japonica* from patients with PV refractory to treatment. *M. globose* in the mycelial phase is the causative agent of typical and disseminated PV [8].

EPIDEMIOLOGY

Pityriasis versicolor has a worldwide distribution, affects all races, and is most prevalent in tropical and subtropical regions, where high humidity and temperature increase disease prevalence [9]. It may affect 40–50% of individuals from specific geographic regions (temperate climates) and ethnic groups [4]. It may occur at any age yet is more common in adolescents and young adults, with a peak incidence between the second and fourth decades of life. In most series, both sexes are equally affected, although there may be a slight male predominance depending on the series studied [1,4].

Numerous epidemiological studies have been conducted globally, with *M. globosa* being the principal etiological agent in regions with a temperate climate; in tropical and subtropical climate regions, the most common species are *M. sympodialis*, *M. furfur*, and *M. globose* [9-11].

PATHOGENESIS

The factors involved in transforming the yeast into its pathogenic mycelial form are uncertain. Endogenous and exogenous factors include genetic inheritance, congenital or acquired immunosuppression, malnutrition, oral contraceptives and corticosteroids, hyperhidrosis, endocrine disorders, elevated temperature, humidity, occlusive clothing, use of oil or moisturizers on the skin, as well as the chemical sebum composition [12].

Malassezia yeasts are lipophilic fungi with a high dependence on a lipid-rich microenvironment, and these microorganisms are part of the skin microbiome [13]. Under certain conditions, the yeasts become a pathogenic agent and produce various skin diseases, even systemic diseases. These fungi are mainly found in the infundibulum of the sebaceous glands, where lipids are widely available. It often requires peptone-rich media to grow, containing short-chain fatty acids (*M. pachydermatis*, *M. furfur*) [14,15].

The virulence factors of these yeasts, intrinsic factors of the host, and extrinsic environmental factors are involved in the pathogenesis of PV. The *Malassezia* cell wall represents the initial point of interaction between the host and pathogen. Its composition is strongly associated with adherence and penetration to tissues, helping it evade host defenses. The cell wall of *M. furfur* and *M. pachydermatis* is mostly galactomannans (galactose and mannose) and glucose [14,15].

Adhesion to host cells is necessary for colonization and infection. In addition to the cell wall characteristics, it also exhibits hydrophobic cell surface characteristics, which promote biofilm formation on biological surfaces and inert surfaces in approx. forty-eight hours in polyurethane catheters. This property gives it increased virulence, resistance to antifungal penetration, and drug resistance, which seems to be associated with the production of systemic infections. Numerous microorganisms generate hydrolytic enzymes that help them in their pathogenicity [13-15]. *Malassezia* species may produce proteinases, lipases, phospholipases, hyaluronidases, and chondroitinsulfatases, which promote the formation of pores in cell membranes, dismantling cell function, and promoting tissue invasion, with the subsequent dispersal of organisms. These lipases destroy triglycerides in the sebaceous glands and produce numerous unsaturated free fatty acids, local irritants, and immunostimulants [12-15]. Complex interaction begins once the yeasts encounter the stratum corneum and colonize it. It has been seen that the *Malassezia* species, under normal conditions, favor the production of transforming growth factor β1 and interleukin (IL) 10, which are powerful immunomodulatory and immunosuppressants decreasing the local response against these yeasts and facilitate the colonization of the skin [12,15].

Once the yeasts penetrate the stratum corneum, these are recognized and phagocytosed by local dendritic cells or Langerhans cells, which recognize and process mannose receptors and present to B and T cells in lymph nodes [1,7,12]. The importance of this T response is reflected in patients with HIV, in whom there is a significant proliferation of *Malassezia* and, in addition, the appearance of seborrheic dermatitis that is difficult to control, related to lymphopenia. It has also been seen that a specific group of patients may have an idiosyncratic response to the *Malassezia* species that favor a type IV hypersensitivity reaction, resulting in a TH1-type response, in addition to increased activity of metalloproteinases, which are potent inhibitors

of elastic fiber synthesis, resulting in atrophic skin lesions [1,16,17].

Malassezia is able to convert tryptophan to a wide variety of indole compounds associated with some of the clinical features of PV, such as the hypopigmentation seen in some lesions. This has been linked to the induction of melanocyte apoptosis, mediated by the activation of the aryl hydrocarbon receptor, which results in the transcription of cytochrome p450 proteins and the stimulation of the caspase pathway [18]. This clinical phenomenon (hypopigmentation) is also explained by the production of azelaic acid, which inhibits the synthesis of tyrosinase, an enzyme that mediates the conversion of L-DOPA to melanin [14]. On the other hand, in ultrastructural studies, it has been observed that some lesions exhibit a decrease in the number, size, and distribution of melanosomes, which would also explain the hypochromic described above. Although indeed, the exact cause of the hyperpigmented variant is unknown, it is suspected to be due to an increase in the thickness of the epidermis, as well as a more remarkable lesional inflammatory infiltrate, which would stimulate the melanocytes to produce more pigment and culminate with an increase in the number, size, and distribution of melanosomes [14].

CLINICAL MANIFESTATION

The lesions include round or oval macules, papules, or isolated plaques that may coalesce and cover large body areas separated by normal skin, leading to pigmentary changes from hypochromic macules (mainly related to the increased production of *Malassezia*-derived dicarboxylic acids, including azelaic acid with the competitive inhibition of tyrosinase) to erythematous or hyperchromic lesions (due to abnormally large melanosomes) [14,17]. Patches of PV have a brown or yellowish color and, if scraped with the fingernail, furfuraceous scaling is observed (Besnier's sign or scratch sign). Zireli's sign is characterized by scaling when the skin is stretched, and it is pathognomonic of PV [1] (Figs. 1 and 2).

DIAGNOSIS

The diagnosis is based on typical clinical manifestations combined with bright yellow fluorescence under Wood's light and direct mycological examination. The methods of lesion scraping or adhesive tape may be employed for material collection and observation under an optical microscope [5]. Potassium hydroxide (10% to 20%) with methylene blue 1% or Albert solution (toluidine blue and malachite green) is used for better visualization of fungal structures. On direct examination, yeast cells and hyphae are easily identified [19]. Vitiligo,

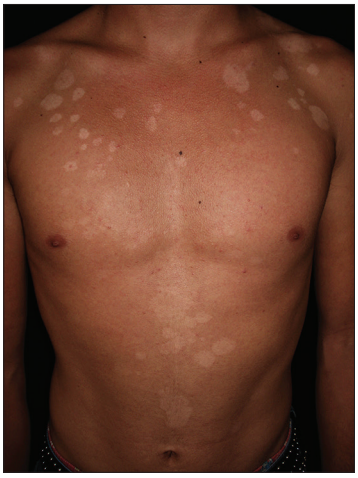

Figure 1: Extensive hypochrominant pityriasis versicolor.

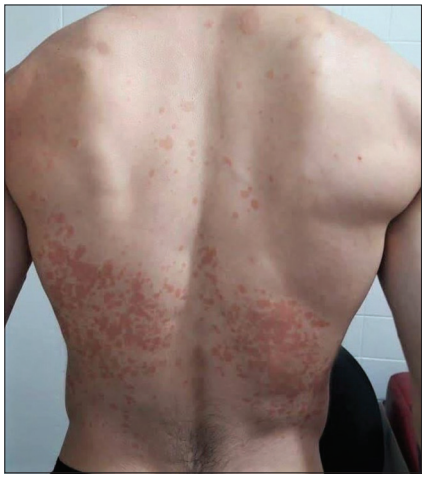

Figure 2: Extensive hypercromiant and recidivant pityriasis versicolor.

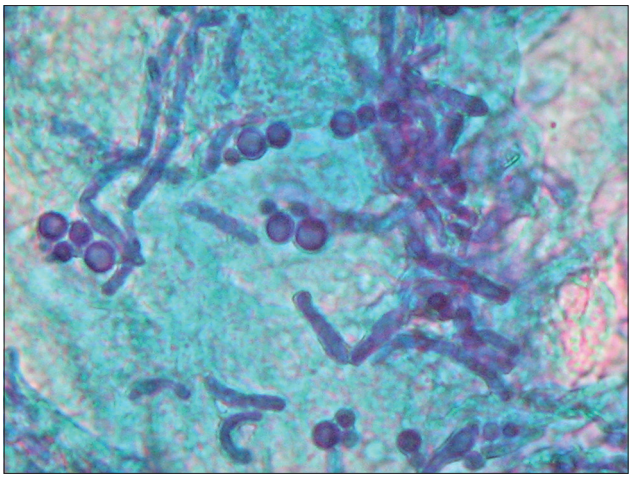

Figure 3: Direct examination: yeasts and short filaments (Albert's solution; 40×).

Table 1: Studies published between 2011 and 2021 on topical and systemic antifungal and non-antifungal treatments.

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
				Topical antifungal thera Romero py				
Dylag M [1]/2020/Poland/1	CR	50	Male	Ciclopirox 1% cream once daily and terbinafine 1% emulsion gel once daily	*M.furfur and M. sympodialis*	14/7 respectively	Direct microscopy examination Two weeks after completed treatment, still revealed fragments of pseudohyphae and single degenerated cells, while the cultures on modified Leeming-Notman agar (MLNA) was negative	No relapse during 8-month follow-up
Abdollahimajd F [2]/2019/Iran/2	CR	Eight months	Female	1% clotrimazole lotion (twice a day)	--	28	Lesions still present and less severity and KOH smears showed negative results for fungal elements	ND
	CR	Four months	Female	1% clotrimazole lotion (twice a day)	--	28	Lesions still present and less severity and KOH smears showed negative results for fungal elements	ND
Gobbato AA [3]/2015/Brazil/60	R, DB, CT	32.5	20/10	Dapaconazole tosylate cream 2%	--	28	Clinical and mycological cure *** (92.6%/84.6%, respectively)	ND
		34.5	15/15	Ketoconazole 2% cream				
Sharma J [4]/2018/India/60	O, R, CT	Comparable	Comparable	Eberconazole 1% cream once daily Terbinafine 1% cream once daily	--	14	Completely healed *** (80/63.33); mild residual disease (20/33.33). Considerable residual disease (0/3.33), respectively	Relapse in 1 patient (terbinafine) at eight weeks.
Ryu HW [5]/2011/Korea/1	CR	29	Male	Topical fluconazole and isoconazole	--	ND	Good clinical results.	ND
Romano C [6]/2015/Italy/1	CR	27	Female	Topical imidazole antimycotic	*M globosa*	28	Clinical and mycological recovery	ND
Marinello E [7]/2017/Italy/1	CR	42	Female	Topical ketoconazole 2% cream	--	42	Skin lesions and the atrophy completely resolved	No recurrence after Three months.
Dioussé P [8]/2017/Senegal/2	CR	18 months	Male	Topical ketoconazole once daily	--	56	Macules had regressed entirely, leaving hypochromia	ND
		12 months	Male	Topical ketoconazole once daily				
Sarkar S [9]/2016/India/80	CT	42 (52.5%) between 21 and 40 years of age	55/25	Ketoconazole 2% cream twice daily Topical luliconazole 1% cream twice daily	--	28	Mycological cure *** (72.50%/92.50%, respectively)	ND
Day T [10]/2014/Australia/1	CR	24	Female	Topical ketoconazole twice daily	--	21	Tan color faded gradually, disappearing by four months	No recurrence to date
Rad F [11]/2014/Iran/90	R, SB, CT	27.25 ± 8.46	56/34	Terbinafine hydrochloride 1% cream twice daily	--	14	Cure rates: *** 81.2/69 (4 weeks);. 70.8/61.9 (8 weeks), respectively.	The recurrence rate at the end of the eighth week: 1.3%/2.4%, respectively
		26.26 ± 8.6		Ketoconazole 2% cream twice daily				

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
				Systemic Antifungal				
Helou J [12]/2014/France/1	CR	52	Male	Itraconazole 200 mg/day one week but not cured Fluconazole 300 mg/week with partial improvement at two weeks Fluconazole 300 mg/week for one month combined with terbinafine twice daily for two weeks	--	49	Total clearance after three treatment schemes.	Relapse after one year
Brandi N [13]/2019/Italy/10	CR	18–38	2/8	Fluconazole 200 mg/day¸ ketoconazole shampoo and a topical antifungal in cream	--	14	Reddish-brown plaques gradually faded within 3-4 weeks, while the pink-white ones remained clinically stable, with negative mycology after one month.	ND
Alam HS [14]/2021/US/1	CR	52	Male	Fluconazole 300 mg/ weekly and ketoconazole 2% shampoo	--	14	At the 6-month follow-up, the tinea versicolor was resolved.	No relapse after six months.
Badri T [15]/2016/Tunisia/71	CT	29.1	20/16 19/16	Fluconazole and ketoconazole shampoo Fluconazole	--	14,28,56	*** 14 days (83/70), 28 days (63/86), 56 days (75/100), respectively.	The highest reinfection rate at the follow-up evaluation occurred in the fluconazole group. Relapse in 18/35 and 15/36, respectively
Balestri R [16]/2012/Italy/7	CR	52.3	5/2	Miconazole nitrate cream twice daily; fluconazole, 300 mg/week	--	28-21	Complete resolution in only 1 patient; complete resolution, respectively.	ND
Sharma M [17]/2014/India/1	CR	22	Male	Fluconazole 400 mg single dose; clotrimazole 1% cream twice a day	--	21	No change in the hypopigmented skin color was noted, but the mycological cure	ND
Jubert E [18]/2015/India/1	CR	32 + 3 weeks of gestational age	Male	Intravenous fluconazole	--	14	Total resolution of the lesions on follow-up after three months with no post-inflammatory hypopigmentation.	ND
Li [19]/2021/US/1	CR	58	Male	Fluconazole 200 mg daily on day 1, followed by 100 mg daily for six additional days	--	7	The rashes resolved within days.	No relapse after 1-year follow-up.
El-Housiny S [20]/2018/Egypt/30	R, CT	--	30/0	Gel 2 (1% Carpobol gel containing: solid lipid nanoparticles of 10% Compritol 888ATO 0.5%, Cremophor RH40, 1% fluconazole) twice daily	--	28	Clinical and mycological cure rates against marketed cream ranged from 40 to 98/36 to 99/22 to 80.	ND

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
				Gel 3 (1% Carpobol gel containing: solid lipid nanoparticles of 10%PrecirolATO5,0.5% Ploxamer 407,1% fluconazole) twice daily Clotrimazole 1% cream twice daily				
Romero-Sandoval K [21]/2017/ Brazil/16	CT	--	11/5	Itraconazole 100 mg daily for 28 days Itraconazole 200 mg daily for 7 days Itraconazole 200 mg daily for 28 days Ketoconazole 200 mg daily for 28 days	*M. japonica (30), M. furfur (30), M. sympodialis (20), M. sloofiae 10), and M. obtuse (10).*	7-28	Clinical improvement (0/0/28.5/50); No response (93.7/100/42.9/20); clinical and mycological cure (6.3/0/28.5/30), respectively.	ND
Choi E [22]/2020/Singapore/1	CR	24	Male	Itraconazole 200 mg for one week, followed by 100 mg for three weeks	--	28	Successful eradication of disease	ND
Allegue F [23]/2017/Spain/1	CR	28	Male	Itraconazole 200 mg daily for one week, topical flutrimazole for four weeks	--	28	Complete resolution after six months	No relapse one year follow up
Cam [24]/2019/Italy/240	CT	--	156/84	Fluconazole 300 mg a week and 2% ketoconazole foam twice a week for two weeks Itraconazole 200 mg daily for one week Ketoconazole 2% foam daily for two weeks	--	28	Clinical cure *** (62.4/36.3/37.5). Negative mycological examination (81.3/66.3/60.0), respectively	ND
Wahab MA [25]/2020/Bangladesh/200	O, R, CT	--	150/50	Itraconazole 200 mg daily Preventive treatment: Itraconazole 200 mg twice daily monthly for six consecutive months Preventive treatment: Placebo monthly for six consecutive months	--	7	Open treatment with itraconazole: Clinical improvement: 90%; negative Wood's lamp examination: 86.5%; mycological cure: 85.5%.	Preventive treatment versus placebo: 81(90%)/ 44(55%); 76(84.4%)/ 41(51.3%); 75(83.3%)/ 42(52.5%), respectively.
Bossini B [26]/2022/Italy/1	CR	15	Female	Oral fluconazole	--	14	Cure	--
Cantrell WC [27]/ 2014/USA/10	O, CT	21 and older		Ketoconazole 2% foam twice daily	--	14	Three out of ten evaluable subjects had negative skin samples. Four additional subjects tested negative at week 4.	1 of 3 relapsed at the week four follow-up visit

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
Dehghan M [28]/2010/Iran/105	R, DB, CT	24.9 5.1	20/30	Fluconazole 400mg single dose.	*M. furfur*	14	Complete clinical response: *** 30% and 49.1; Incomplete response: 66% and 47.3%. No response 4% and 3.6%.	Recurrence or no clinical response was seen in three cases (6%).
		24.1 5.9	21/34	Clotrimazole cream twice daily				
				Non-antifungal treatment				
Carmo ES [29]/2013/Brazil/48	R, CT	32.8	10/20	Cymbopogon citratus essential oil	*M. sympodialis* (33/33); *M. furfur* (26.7/11.1); *M.obtusa (3.3/-); M. globose (-/5.5); M. sloofiae (-/5.5)*	40	Mycological cure *** (60/90, respectively)	None
		33.5	10/8	Ketoconazole 2%				
Bakr E [30]/2020/Egypt/90	R, CT	29.9	22/8	Ketoconazole cream 2%	ND	28	Significantly improved (83.3/70/93.3); improved (13.3/16.7/6.7); Slightly improved (3.3, 13.3/0), respectively; no unchanged or aggravated cases were seen	ND
		29.8	19/11	Adapalene gel 0.1%				
		29.1	26/4	Combined treatment				
Balevi A [31]/2018/Turkey/38	CT	30.63 ± 12.03	26/12	Narrow-band UVB phototherapy 3x/weekly	--	Until complete clearing or to a maximum of 56 days	66.7% achieved excellent results; 14% had the mild residual disease; In 20% had improved lesions were <50%, and the KOH test was positive	16.6% of the good responders relapsed two months after the end of phototherapy.
Shi TW [32]/2015/China/95	R, CT	25.8 ± 6.5/2	56/44	Adapalene 0.1% gel and ketoconazole 2% cream once daily	--	14	Total improvement rate (92% significantly improved/72% improved)	ND
		28.5 ± 7.3		Ketoconazole 2% cream twice daily				
Khattab FM [33]/2021/Egypt/26 unresponsive	R, CT	29 ± 903	14/10	Excimer laser (308 nm three times weekly)	*Malassezia furfur* (61), *M. globose* (19), *M. sympodialis (16), M. restricta (4)*	56	Total improvement rate (91.6)	Follow-up for ten months: 8.3% of recurrence rate
				Topical placebo				
Nashwa RK [34]/2020/ Egypt/120	CT	Range 12-40	52/68	Weekly tea tree oil-saturated human amniotic membrane	--	56	Clinically healed *** (78.3/55)	No relapse three months post healing
				Tioconazole 1% cream daily				
Sepaskhah M [35]/2016/Iran/50	DB, R	30± 8.9	--	Tacrolimus 0.03% ointment twice daily	--	21	Complete global cure (14 [56]/ 14 [56]); Partial cure (3 [12]/ 1 [4]); Failure (8 [32]/ 10 [40]), respectively.	ND
		30±9.6		Clotrimazole 1% cream twice daily				
Alberdi E [36]/2020/Spain/4	CR	43.2 ± 10.7	0/4	Photodynamic therapy with methylene blue	--	28	Complete clinical and mycological cures were observed in all patients.	Relapse was not seen in the 6month follow-up

(Contd...)

Table 1: *(Continued)*

Author [Ref] year/ country/N	Study Design **	Age (yrs. ± SD)	Sex (M/F)	Drug/Substance	Agents (%)	Treatment Period (days)	Outcome	Relapse
Lone AH [37]/2012/India/40	SB, R	30.2	34/6	Polyherbal formulation topically twice daily	--	30	Effective treatment: 19 (95)/18(90); mycological cure: 20 (100)/20(100); Not cured: 1(5)/2(10), respectively	After the completion of treatment (30 days), all became negative for KOH examination on the 30th-day assessment
		31.3		Sodium thiosulphate lotion (20%) locally twice a day				
Jowkar F [38]/2010/Iran/64	DB, CT	21 (13–28)	31/33	3% sodium nitrite (nitric oxide-liberating) cream with 3% salicylic acid, twice daily 3% salicylic acid cream (placebo)	--	10	Cured: 87.5% and 43.8% *** Uncured: 12.5% and 56.2%	ND

*Disseminated pityriasis versicolor with more than four relapsing episodes in twelve months.
**DB: double-blind; SB: single-blind; O: open; R: randomized; CT: clinical trial; CR: case report.
***Statistically significant: $p < .05$.
ND: Not determined.

pityriasis alba, hypochromic mycosis fungoides, and postinflammatory hypopigmentation should be considered in the differential diagnosis [20] (Fig. 3).

TREATMENT

We detected several systematic reviews focused on the different topical and systemic treatment options in the management of PV (Table 1). The four most important reviews in the search parameters focus on the efficacy of topical ketoconazole, and in cases that require systemic management, the best options are itraconazole and fluconazole [21-24]. The lesions may be recurrent or recalcitrant to antifungal treatments [21,25]. Recurrent cases include extensive or disseminated cases with atypical variants related to infectious agents such as *M. japonica* and elevated IgE levels [7,26].

Pityriasis versicolor may persist chronically if left untreated. Numerous topical and oral antifungal treatments effectively alleviate clinical symptoms and lead to mycological cure. First-line treatment includes topical antifungal therapy [27]. Topical azole antifungals are effective for PV, and no significant difference in the efficacy of different azoles is observed. Ketoconazole shampoo, selenium sulfide, or zinc pyrithione are recommended in hairy areas; due to the difficulty of applying the antifungal cream, these are applied to the skin in a shower and washed off after 3 to 4 minutes for 2–3 weeks [28]. Terbinafine 1% cream and ketoconazole 2% cream are adequate, similar to new antifungals such as topical fluconazole. The usual treatment time is 2 to 3 weeks [29].

Based on evidence, treatment once or twice daily for fourteen days with topical ketoconazole cream or foam and once-weekly ketoconazole shampoo may be effective for PV with long-term efficacy. Similarly, terbinafine 1% cream should be applied twice daily for seven days [21]. Keratolytic soaps, such as sulfur-salicylic acid soaps, demonstrated a 62% cure rate and had the best results with extended duration of application, yet when compared to 1% clotrimazole, the latter had better results [30].

Shi et al. [31] compared ketoconazole 1% cream as monotherapy with ketoconazole cream combined with adapalene 1% gel. Adapalene is a naphthoic acid derivative indicated for treating acne vulgaris, because it binds to retinoic acid receptors (RAR) located mainly in the skin and epidermis (RARb and RARg, respectively), inhibiting cell differentiation. This study defined the

total improvement rate as negative direct microscopy and a clinical improvement of 50% four weeks after treatment. The combined treatment significantly improved (92% vs. 72%, respectively; $p = 0.0009$). In a study by Bakr et al. [32], the response to treatment was significantly different when the combined treatment of ketoconazole 2% cream and adapalene 0.1% gel was administered as compared to the treatments as monotherapy at seven weeks (93.3/70/83.3, respectively).

Regardless of the medication administered, the normalization of pigmentation may take several months after the completion of treatment [1,2].

RECURRENT PV

Although the infection does not represent a significant health risk to the affected individual, the psychological and social implications may be profound. The disease becomes chronic without treatment. A relapsing disease tends to recur in around 60% of the cases within a year after treatment. Spontaneous remissions are rare [3].

It is also described as recurrent, recalcitrant, or relapsing PV. The disease evolves in outbreaks, with the improvement and aggravation of the symptoms, leading to relapse. Due to several predisposing factors, relapse is a significant problem. PV may recur after incomplete antifungal treatments [2,3]. Faergemann reported a relapse rate of 60% after one year and 80% after two years of treatment [33]. Relapse probably occurs due to the presence of yeasts in the sebaceous follicles and several predisposing factors that allow the multiplication and filamentation (hyphae formation) of yeasts. During the twenty-month follow-up, relapse was observed in periods of excessive sweating caused by physical exercise or after spending time at the beach, pool, and farm. The patients also associated relapses with higher temperatures (summer) or the application of oily products to the body (moisturizers, sunscreens). The patients with PV with one to four relapsing episodes in twelve months were classified as having relapsing PV [3].

Drug resistance is another increasing problem affecting all antifungal agents [34]. Azole resistance may be primary (intrinsic) or secondary (acquired). The former is found naturally without prior (known) antifungal exposure. The latter results from a previously susceptible strain exposed to antifungals or other selective pressure and may result from altered gene expression, point mutations, or allelic variations. Both may be attributed to an increase in 1) the prophylactic use of azole drugs, 2) prolonged treatment regimens, 3) agricultural use of azole fungicides, or 4) the broad-spectrum, long-term, and low-dose use of azoles in consumer care. As an example, azole resistance has been extensively studied for *Aspergillus fumigatus*. It develops either during treatment at the hospital or following intensive agricultural practice [35]. The environmental route of resistance development has been reported since 2007 [35]. *Malassezia* azole resistance is associated mainly with mutations in the ERG11 gene, identified from clinical isolates [36].

TREATMENT OF RECURRENT PV

In recurrent, disseminated, or recalcitrant cases with topical therapy or patients who experience multiple relapses, oral itraconazole 100 mg daily for fourteen days may be a practical option [37]. Oral fluconazole is also effective and safe [38,39]. The cure rate ranged from 78% to 98% when fluconazole was started once weekly for two weeks [38]. A randomized controlled trial on adults demonstrated that a single high-dose (400 mg) fluconazole treatment may be more effective than itraconazole (65% vs. 20%, respectively); the relapse rate was 35% in the fluconazole group and 60% in the itraconazole group at the end of eight-weeks follow-up [39].

Other treatment options, including adapalene gel with ketoconazole cream [31,32], increase the success rate of topical ketoconazole cream from 72% to 92% [31].

Ali Balevi et al [40] showed that narrow-band UV-B is an effective and safe alternative for managing extensive and recurrent PV. It is suggested for PV cases, unresponsive to conventional treatments or not suitable for systemic antifungal treatments.

Other reported options include topical tacrolimus 0.03%, showing similar clinical and mycological cure rates to clotrimazole 1% cream in cases of PV [41]. Bartell et al. [42] reported the case of a fourteen-year-old male with recurrent PV, who was treated with isotretinoin for acne vulgaris and had complete remission of the mycosis. This favorable response was probably due to the excessive sebum production in the pathogenesis of PV, allowing for novel therapies.

A prophylactic regimen may delay or avoid PV recurrence. Prophylactic regimens using ketoconazole include 200 mg given on three consecutive days every month or a single dose of 400 mg taken once a month; itraconazole is also a reliable option for prophylaxis [43].

CONCLUSION

The prevention of the recurrence of infections is essential, including superficial infections such as PV. There are currently numerous topical and oral antifungal treatments that effectively reduce the recurrence, leading to clinical and mycological cure. Topical therapy is the first line of treatment for PV in uncomplicated cases of PV. When topical treatment is not feasible or practical, itraconazole and fluconazole are viable options, with pramiconazole as a potential new therapy. In addition to antifungal therapies, non-antifungal treatments have shown efficacy in cases of recurrent PV and could be employed as maintenance or preventive therapy.

The advantages of topical treatment include fast acting, well toleration, smaller risk of severe adverse effects, and limited drug interactions. This is especially evident with the use of ketoconazole. Multiple applications of topical medications may increase adverse events and limit patient compliance, especially in cases of PV in which large body areas are affected. In these cases, oral antifungal may be preferable for many patients, and short courses of oral treatments are the most reliable option. Relapse is common, and thus prophylactic treatment may be necessary to relieve symptoms, especially in recurrent PV.

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Source of Support: This article has no funding source.

Conflict of Interest: The authors have no conflict of interest to declare.