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Treatment Failure in Scabies: Assessment of Risk Factors in a Multicenter Cross-Sectional Study

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ABSTRACT

Introduction: Recent reports of increased prevalence and treatment failure in scabies have raised concerns worldwide. Drug efficacy as well as adherence to treatment are important in treatment failure, and data on the latter are limited.

Objective: We aimed to determine the factors associated with treatment failure in scabies.

Methods: This prospective, multicenter observational study was conducted in three centers, enrolling 230 patients diagnosed with scabies. Treatment outcomes were assessed one month after treatment initiation. Patients completed a questionnaire evaluating factors potentially affecting treatment outcomes. Demographic and clinical characteristics and adherence to treatment recommendations were compared in two groups: successful treatment and treatment failure.

Results: The study included 125 males and 105 females, with a mean age of 24.6 ±17.6 years. Treatment failure was found in 58 patients (25.2%). No demographic parameter or medication was associated with treatment failure. Three independent risk factors for treatment failure (multivariate regression analysis) were lack of application of topical medication to the whole body, (odds ration (OR): 14.33; 95% confidence interval (CI): 2.9–71.4), lack of reapplication after washing hands (OR: 3.5; 95% CI: 1.5–8.0), and not reading of the information form (OR: 13.7; 95% CI: 1.3–80.6).

Conclusion: Treatment failure in scabies is quite common. Incorrect or incomplete application of topical treatment and lack of hygiene measures are the main factors leading to treatment failure. Providing a written information sheet with step-by-step treatment recommendations may contribute to treatment success.

Introduction

Scabies is a highly contagious ectoparasitic disease caused by *Sarcoptes scabiei* var. *hominis* [1]. It primarily spreads through close skin-to-skin contact with an infected individual and less commonly through contaminated objects and clothing [2]. The World Health Organization (WHO) has designated scabies a Neglected Tropical Disease and one of the most common dermatological diseases in developing countries, affecting approximately 400 million people worldwide each year [1].

Scabies are more prevalent in certain geographical areas, including hot, tropical countries, regions with limited water resources, low-income countries, and in special groups such as large families, children, immigrants, and immunosuppressed patients. However, growing data suggest that the scabies outbreaks happen in populations without these risk factors and in some high-income countries [3,4]. In recent years, several studies have also reported a rise in the incidence of scabies in Turkey [5,6].

Clinical diagnosis of scabies has become significantly easier and more practical with the use of dermoscopy in daily practice. Various oral and topical treatment options for scabies are now available in most countries. Despite these diagnostic and treatment advantages, epidemics continue to occur, as in our country [3,4]. It seems necessary to address all potential gaps in patient management, such as drug resistance, inappropriate treatment practices, lack of hygiene practices, and re-infestation. A recent meta-analysis reported drug-related treatment failure as 15.2%, although some studies have reported that this rate increased to 53.3% [7]. The several studies investigating the factors associated with treatment failure have indicated that treatment failure may be related not only to the ineffectiveness of the drugs used but also to additional factors [8-11].

Objective

We aimed to investigate the factors associated with treatment failure in scabies, including demographic, clinical, and treatment-related factors, including topical medications, application, and hygiene measures.

Methods

This multicenter prospective observational study was conducted between January 2022 and June 2023 at three different dermatology clinics. A total of 230 patients diagnosed with scabies were involved in the study. In all patients, diagnosis of scabies was confirmed by a microscopic (applying potassium hydroxide to epidermal scraps to identify scabies mites, eggs, and/or feces under a light microscope) or dermoscopic examination (visualizing scabies mites and/or eggs using dermoscopy) [12].

Baseline visit

At baseline, patient records included demographic and clinical findings, living and environmental conditions, and previous treatments after diagnosis of scabies. Based on the patients, clinical and social features and on the physician's decision, one of the following therapies were administered; permethrin 5%, precipitated sulfur ointment 10%, or a combination treatment (tar cade oil 12.5%-sulfur 12.5%, permethrin 5%-precipitated sulfur ointment 10% or permethrin 5%-tar cade oil 12.5%-sulfur 12.5%). Due to local regulations, only one patient used oral ivermectin during the study period. All patients were verbally informed about how to use the related medication and personal and environmental hygiene processes. Furthermore, all patients were advised to read and follow the information sheets provided, which outlined drug application procedures, including application times, body parts to be applied, and personal and environmental hygiene measures, including cleaning of clothes and house. These sheets were prepared in line with guideline recommendations [2,13-15].

Second Visit (Control visit)

The control visits were performed one month after the baseline visit. Patients were evaluated and examined for scabies symptoms by the dermatologist who had previously examined that patient. Successful treatment was defined as the complete resolution of previous symptoms and the absence of any evidence of scabies on microscopic or dermoscopic examination. Treatment failure was defined as the presence of symptoms and signs of scabies and confirmation of disease using microscopic and/or dermoscopic examination. Nodular lesions were evaluated by dermoscopic examination, and successful treatment was considered if there was no evidence of active infestation. Pruritus related to xerosis-irritation caused by topical medications that persisted after treatment was distinguished from active infestation by detailed examination and history. Additionally, patients were assessed on their adherence to medication instructions, whether they had read the provided information sheets, and their compliance with hygiene recommendations. In this assessment, the physician used standardized questionnaires; however, individual variations in the responses could not be completely eliminated.

Patients were divided into two groups: those with "successful treatment" and those with "treatment failure". These two groups were compared in terms of demographic, clinical, lifestyle, and environmental characteristics (Table 1).

Table 1. Demographic and Clinical Features of Successful Treatment and Treatment Failure Groups.

	Total Number of Patients (N=230)	Successful Treatment (N=172)	Treatment Failure (N=58)	P
Demographic features				
Sex, N (%) Male Female	 125 (54.3) 105 (45.7)	 96 (55.8) 76 (44.2)	 29 (50.0) 29 (50.0)	0.442
Age, mean (SD)	24.6 ±17.6 20 (0-74)	25.2±17.2 21 (0-74)	22.5±18.8 18 (1-71)	0.311
Age group, ≥18 age	136 (59.1)	106 (61.6)	30 (51.7)	0.217
Comorbidities, n (%)				
Systemic disease*	46 (20.0)	33 (19.2)	13 (22.4)	0.595
Immunsuppression	7 (3.0)	7 (4.1)	0 (0)	0.196
Dermatological disease**	13 (5.7)	9 (5.2)	4 (6.9)	0.742
Atopic dermatitis	8 (3.5)	7 (4.1)	1 (1.7)	0.683
Scabies history				
Disease duration, day, mean (SD)	50.9±116.9 0 (0-900)	45.9±105.6 0 (0-900)	65.7±145.5 0 (0-730)	0.267
Time from onset of symptoms to diagnosis, day, mean (SD)	42.8±69.2 30 (0-700)	38.4±61.5 30 (0-700)	55.8±87.3 30 (3-540)	0.097
Lifestyle and environmental characteristics, n (%)				
Having a baby	33 (14.3)	20 (11.6)	13 (22.4)	**0.043**
Having an elderly or bedridden person	27 (11.7)	18 (10.5)	9 (15.5)	0.301
Having someone with pruritus	185 (80.4)	137 (79.7)	48 (82.8)	0.704
Having a household member with scabies	98 (42.8)	73 (42.7)	25 (43.1)	0.956
Having an immunosuppressed patient	8 (3.5)	7 (4.1)	1 (1.7)	0.683
Treatment, n (%)				
Permethrin 5%	129 (56.1)	90 (52.3)	39 (67.2)	0.066
Precipitated sulfur 10%	115 (50.0)	88 (51.2)	27 (46.6)	0.544
Oral ivermectin	1 (0.4)	1 (0.6)	0 (0)	1.00
Topical corticosteroid	2 (0.9)	2 (1.2)	0 (0)	0.162
Combination treatment***	60 (26.3)	47 (27.6)	13 (22.5)	0.097
Details on topical treatment, n (%)				
Whole body, including between the toes, genital area	213 (92.6)	170 (98.8)	43 (74.1)	**<0.001**
Reapplication to the hands after washing	181 (78.7)	147 (85.5)	34 (58.6)	**<0.001**
Other treatment-related parameters, n (%)				
Information sheets unread	11 (4.8)	2 (1.2)	9 (15.5)	**<0.001**
Nonadherence to cleaning recommendations	36 (15.7)	18 (10.5)	18 (31.0)	**0.001**
Successful treatment of close contacts	210 (91.7)	163 (94.8)	48 (82.8)	**0.004**

* Diabetes mellitus, hypertension, bronchial asthma , hypothyroidism and others.

** Psoriasis vulgaris, seborrheic dermatitis, lichen planus, acne vulga,ris, hand eczema, acne rosacea.

*** Tar cade oil 12.5%+ precipitated sulfur 12.5% or permethrin 5%+precipitated sulfur ointment 10% or permethrin 5%+tar cade oil 12.5%+ precipitated sulfur 12.5%.

Table 2. Multivariate Analysis to Identify Independent Risk Factors Associated With Treatment Failure.

Variables	P	OR	95%CI
Having a baby (<2 years) at home	0.13	0.32	0.130-0.790
Application of the medication to the whole body, including between the toes, genital area	**0.001**	14.33	2.875-71.426
Re-application of the medication to the hands after washing them for any reason	**0.003**	3.47	1.516-7.978
Having a household member with scabies	0.253	2.03	0.602-6.878
Reading the information sheet	**0.004**	13.67	1.321-80.555
Correct implementation of cleaning recommendations	0.224	1.78	0.701-4.548

Logistic regression analysis was used to define independent risk factors. Abbreviations: CI: confidence interval; OR: odds ratio.

The study was approved by the local ethics committee at the İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye (approval number:1065/2022) and was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using SPSS software version 15 (SPSS Inc., Chicago, Illinois, USA). The descriptive statistics comprise the mean, standard deviation, minimum and maximum scores for the numerical variables, and numbers and percentages for the categorical variables. Comparison of independent variables between the two groups was made using Student's t-test for normal distribution and Mann-Whitney U test for those not showing normal distribution. For comparisons of more than two groups, the Kruskal-Wallis test was used. A logistic regression analysis was used to estimate ORs and 95% CIs for the association between the presence of treatment failure and risk factors found to be statistically significant (P<0.05) in univariate analysis.

Results

A total of 230 patients, 125 males (54.3%) and 105 females (45.7%), with a median age of 20 years (range 0–74) were included in the study. The mean time from the onset of symptoms to scabies diagnosis was 42.8±69.2 days, and the mean time from the initial diagnosis was 50.9±116.9 days. Detailed demographic characteristics of the patients are summarized in Table 1.

The most commonly applied topical treatments were permethrin (56.1%), precipitated sulfur ointment (50%), and combination therapy (26.3%). Topical medication applications and hygiene practices were evaluated. The majority of the patients (92.6%) had applied the medication properly to the whole body, including between the fingers, genital area, and body folds. However, 78.7% of the patients had reapplied the medicine to their hands after washing their hands for any reason. On average, 4.8% of the patients did not read the information sheets, and 15.7% did not adhere to cleaning/hygiene recommendations (Table 1).

Treatment failure was identified in 58/230 patients (25.2%). No demographic parameter or topical medication was associated with treatment failure. Socioeconomic status was similar in both groups. On the other hand, the following parameters related to the treatment procedures were found to be significantly lower in the treatment failure group; "the whole-body application including between the fingers," "re-applying the medication after washing hands," and "successful treatment of close contacts " (P<0.001, P<0.001, and P=0.004, respectively). Moreover, the treatment failure group included a higher percentage of patients who did not read the information sheet and did not perform appropriate personal and environmental hygiene procedures. The other factor associated with treatment failure was 'having a baby at home' (P=0.043) (Table 1).

Multivariate regression analysis showed a lack of application to the whole body, including between the fingers (OR: 14.33; 95% CI: 2.9–71.4), lack of reapplication after washing hands (OR: 3.5; 95% CI: 1.5–8.0), and not reading the information sheet (OR: 13.7; 95% CI: 1.3–80.6) (Table 2) to be independent risk factors for treatment failure.

Discussion

In the present study, treatment failure was observed in approximately one-quarter of the patients. Incorrect application of the medication and not reading the information sheet were identified as independent risk factors associated with treatment failure. Treatment failure in scabies has been increasingly reported in recent years, ranging from 15.2% to 53.3% [7-9]. This variability may be attributed to differences in relevant patient populations, medications, treatment methods, countries, communities, and study methodologies. Three possible causes for treatment failure

in scabies have been suggested: misuse of the prescribed medications, reinfestation through untreated close contacts and inadequately cleaned clothing, bedding, and furniture, and lastly, resistance of mites to drugs [13]. Identifying which of these factors has led to treatment failure is critical to the management of this annoying disease.

In our study, the most common factor associated with treatment failure was incorrect or incomplete application of topical medications, such as not applying treatment to the entire body, including between the fingers, and not reapplying medication after washing hands. As the guidelines emphasize in detail, the appropriate application of topical treatments is critical to the successful treatment of scabies [2,14-16]. A limited number of studies in the available literature evaluated errors/deficiencies associated with the application of medications in scabies. Ulff et al. used a fluorescent test cream to assess neglected areas during topical medication application. The striking result was that even individuals without physical limitations neglected a third of the target body area [17]. Another study evaluated 21 scabies patients by applying fluorescent cream after being instructed on how to apply the medication [18]. Of these patients, 62% neglected the ankles, 33% neglected the areas between the toes, 24% neglected the sacral area, and none of the patients applied the treatment correctly [18]. Since the use of topical treatments requires a high degree of patient compliance, patients should be instructed on negligible areas and the duration and intervals of application of the drug [2,14]. In some resistant patients, hospitalization and application by a nurse may be considered [18].

Another factor associated with treatment failure in the present study was not reapplying the medication after washing hands (41.4% in the treatment failure group). In an observational study investigating treatment failure in scabies, 58% of patients reported not reapplying medication after washing their hands [11]. Since effective topical treatment in scabies requires that the medication remain on the skin for a certain period, all patients should be instructed to reapply the medication immediately after washing it off or removing it before the recommended time. The latest guidelines also specifically emphasize reapplying scabies medication after washing and drying the hands [14,16]. Another finding of the present study that shows the importance of step-by-step instruction for effective treatment is the correlation between not reading the information sheets and treatment failure. The details of topical medications and additional hygiene measures used in the treatment of scabies can be difficult to remember. Therefore, providing a written form with step-by-step instructions, as recommended by the guidelines, may increase patient compliance and therefore treatment success [2,14].

The development of resistance to drugs used for scabies is a controversial issue, and it is debated whether treatment failure is due to real drug resistance or to incorrect application of drugs. In recent years, studies have reported resistance to permethrin, suggesting that this resistance may be more related to the drug itself than to its improper application [19,20]. Currie et al. identified genetic mutations in voltage-gated sodium channels of the mite that causes permethrin resistance [21]. A recent systematic review and meta-analysis examining treatment failure in scabies revealed that ivermectin and permethrin had lower rates of failure, while a single dose of ivermectin increased the risk of treatment failure compared to two doses [7]. There is also evidence that there is no resistance to permethrin. Yürekli exposed live mites to concentrations of 5%, 7%, and 10% permethrin and found that all tested concentrations were lethal to the parasites [22]. The author emphasized that, rather than resistance to permethrin, treatment failure was most likely due to incorrect application of the medication or lack of effective treatment of family members [22]. In our study, we found no statistically significant difference between the two groups in terms of topical medication options, suggesting that proper application and hygiene measures were more critical to successful treatment than was the type of medication. To assess real drug resistance, studies conducted in homogeneous groups and examining drugs specifically are needed.

Improper or incomplete application of cleaning measures, lack of successful treatment in close contact, and having a baby at home were found to be associated with treatment failure in univariate analysis. These were also factors that had the potential to cause treatment failure through reinfestation.

Several studies have evaluated the causes of treatment failure in scabies. Some of the factors reported are inadequate treatment of close contacts, lack of second treatment within 7–14 days, inadequate effectiveness of current treatments [11], limited mobility and use of topical corticosteroids before diagnosis [9], a delay of more than one month between the onset of pruritus and scabies treatment, the use of single-dose ivermectin, and failure to disinfect objects with acaricides [8]. Magikami et al. reported that impaired immunity and problematic behavior increased the recurrence of scabies [10]. Both our study and the existing literature show that success in treating scabies depends not only on the presenting patient but also on those living with the patient, their behavior, and general cleaning measures.

Limitations

The main limitations of our study include a relatively small number of patients, considering the high prevalence of the disease. Other limitations are the lack of standardization across patient groups and an assessment of baseline disease severity. Variations in demographic characteristics, disease severity, socioeconomic status, sociocultural levels,

and environmental conditions may have impacted the study's outcomes and limited the generalizability of the results. On the other hand, the existence of these variations is valuable in that they represent a cross-section of real-life society.

Finally, the other important point was that the use of systemic ivermectin due to local factors was very limited. The use of ivermectin reduces the likelihood of treatment resistance, so limited use may have increased treatment failure.

Conclusion

Treatment failure for scabies has become a growing global concern affecting individuals across all socioeconomic groups. Our prospective study examining factors associated with treatment failure showed that inappropriate use of topical medication was the major risk factor for treatment failure, regardless of the medication used. In addition, inadequate cleaning of living space, untreated close contact(s), and having a baby at home were also found to be associated with treatment failure. To improve treatment outcomes, we recommend providing patients with written information sheets that outline the treatment process step by step, encouraging them to read; this can increase patient compliance and improve overall success rates.

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