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Original Article

New multiple therapy of resistant and relapsing dermatophyte infections during epidemic status

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Abstract

Background Resistant dermatophytosis is now running in many countries where fungal skin infection is a major health problem like Iraq and neighboring countries.

Objective To evaluate the efficacy of a novel therapeutic regimen in the management of resistant dermatophytosis using multiple drug therapies.

Methods This is a prospective therapeutic research where 400 cases with varying kinds of dermatophytosis were included and managed by new 2 phases of therapy, each four weeks period and as follow: Phase one using combination of oral terbinafine and oral ketoconazole and topical terbinafine cream plus selenium sulfide shampoo. While phase two including combination of oral terbinafine and oral itraconazole and topical terbinafine cream plus ketoconazole shampoo to achieve complete cure rate. Follow-up was done for eight weeks to record relapse of fungal infection.

Results This study included 400 patients with chronic relapsing dermatophytosis, 250 (62.5%) males and 150 (37.5%) females, their ages ranged from 6-70 years. The duration of the disease ranged from 6-32 months with a mean of 11 months. The response to the phase one therapeutic regimen started after 5-7 days by decreasing in the redness, itching, inflammation, and scales. An obvious response was seen at the end of the first two weeks while full complete recovery response was achieved after four weeks. While phase two also showed 100% obvious cure rate. Follow up for eight weeks showed 2% relapse rate. This combination was well tolerated with no serious systemic or topical adverse effects were recorded in most of the patients.

Conclusion This new therapeutic multiple drug therapy is effective in all included types of dermatophytosis especially with chronic resistant course of the disease with very low relapse rate.

Key words
Chronic; dermatophytosis; antifungal ;ketoconazole; terbinafine; itraconazole.

Introduction

Superficial fungal skin infection is a global health issue with 20-25% of the world communities affected by at least one species of Trichophyton (T), Microsporum (M) or Epidermophyton (E).[1,2]

Recently, outbreak of resistant and relapsing dermatophytes infections has been noticed in Iraq and many neighboring countries including Syria and Iran.[3,4]

Dermatophytosis is among the most common infective dermatoses seen in dermatology outpatient clinics. Now, Iraq facing an attack of chronic and relapsing dermatophytosis in volumes never been encountered before and reaching epidemic state as patients were seen from different parts of Iraq from Mosul north to

Basra city south.

In India, there is genuine outbreak of various recalcitrant relapsing dermatophytosis caused by T. mentagrophytes type VIII.[5] And this strain has been noticed upon scrapping of the affected skin in many countries including Iraq, India, Germany and Iran.[4,6-8]

Iraq has been facing a challenging scenario of chronic, relapsing, extensive, odd and recalcitrant superficial fungal skin infections due to type VIII of T. mentagrophytes.[3,6]

In Iraq, recently, there has been a major upsurge of superficial fungal skin infection as well as its atypical clinical presentations and clinical, microscopic examination and culture were used for diagnosis.[3,6]

Clinical resistance to standard treatment with antifungals has been a concern, especially in areas like Iraq, which has observed an emergence of terbinafine- resistant superficial mycoses caused by T. mentagrophytes type VIII.[3,6]

The ordinary standard treatment of dermatophytosis that usually used by Iraqi dermatologists consists of single therapy using oral (fluconazole, itraconazole or griseofulvin) and/ or topical antifungal creams like terbinafine, clotrimazole, micanazole and whitfield ointment and this regimen frequently results in treatment failures and relapses especially when given in standard doses and for conventional period.[9]

In order to overcome treatment failure or relapses, the management of dermatophytes infection is becoming more subjective and based on individual experiences.[10,11] So we tried a combination therapy to decrease the chance of drug resistant and decrease the relapsing rate. This observation has encouraged us to conduct this work using a combination of two regimens for long duration (2 months).

The combination treatment of two or more drugs is a well-known idea of utilizing synergistic effects of these medications to enhance treatment efficiency and handling the possible resistant to drug.[12] The combined synergy of itraconazole and terbinafine has been effective against various dermatophyte and non-dermatophyte infections in vitro studies.[13,14]

Limited studies on oral ketoconazole have shown some safety precautions for its use but by a new extensive research over a huge number of cases proved its safety in treatment of diverse skin diseases mainly dermatophytosis and cutaneous leishmaniasis.[15]

So, the objective of the current work is to assess the efficacy of a novel therapeutic regimen in the management of resistant and relapsing dermatophytosis.

Patients and methods

This is a prospective therapeutic research where 420 patients with varying types of dermatophyte infections were included from March 2016 to April 2021. All enrolled cases had failed to respond to oral and/ or topical antifungal therapy used in standard doses and for conventional

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period.

For the purpose of this study, a diagnosis of "chronic dermatophytosis" was made in patients who have complained from the disease for more than 6 months despite being treated while "recurrent dermatophytosis" refers to the relapse of the dermatophyte infection within four weeks, after stopping antifungal remedies. Patients with only tinea ungium, only tinea capities, immunocompromised state, diabetes mellitus, Cushing's syndrome, those on immunosuppressants medications, left-sided heart disease, patients with liver or kidney disease, pregnant and lactating women were excluded.

A Full history was taken focusing on possible risk factors for chronic or recurrent superficial fungal skin infection such as an intra-family history of fungal infection, a history of contact with pets, and treatment with topical or systemic antifungals or other treatment. The study followed the Declaration of Helsinki and informed consent was taken from each enrolled case, before starting the therapy, after full explaining about the method of treatment, possible complications, follow up, and the need for before and after treatment photographs. The diagnosis was based on clinical pictures established with direct microscopic examination. Skin scrapings from the edge of the lesion or infected hair were gathered and examined microscopically after immersion in 10% potassium hydroxide (KOH). In addition, from April to December 2019, skin scrapings and hair were gathered from 92 cases. These samples were sent to the Laboratory of Medical Microbiology, Mölbis, Germany for mycological diagnostics and sequencing.[6] These cases were treated by new 2 phases of therapy, each four weeks period as follow:

Phase one using combination of oral terbinafine and oral ketoconazole and topical terbinafine cream twice a day plus selenium sulfide shampoo twice a day and watch response to therapy. While phase two including combination of oral terbinafine and oral itraconazole and topical terbinafine cream twice a day plus ketoconazole shampoo twice a day to record relapse rate. Follow-up was done for eight weeks to achieve a full cure of fungal infection.

The dosage of oral terbinafine and ketoconazole was as follow:

Terbinafin: Adults (250 mg/day), children above 2 years old and under 20 kg (62.5 mg/day), children above 2 years old and 20–40 kg (125 mg/day), children above 2 years old and above 40 kg (250 mg/day). While ketoconazole: 200 mg twice/day for adults and 3.3-6.6 mg/kg/day for children. While the dose of oral itraconazol (200mg/day for adults and 3-5mg/kg for children)

Blood samples were taken before initiation of therapy and every 2 weeks for the first month then after the second month for the patients with abnormal laboratory results during follow-up period. The following tests were carried out: alkaline phosphatase (ALP), alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), creatinine, urea, prothrombin time (PT), total bilirubin (TBL), International Normalization Ratio (INR).

Follow-up was done for two months after stopping treatment to record relapse of fungal infection and any possible side effects.

Results

Only 400 patients were enrolled in the present work while 20 patients defaulted for many reasons mainly life difficulties. All patients with chronic relapsing dermatophytosis, 250 (62.5%)

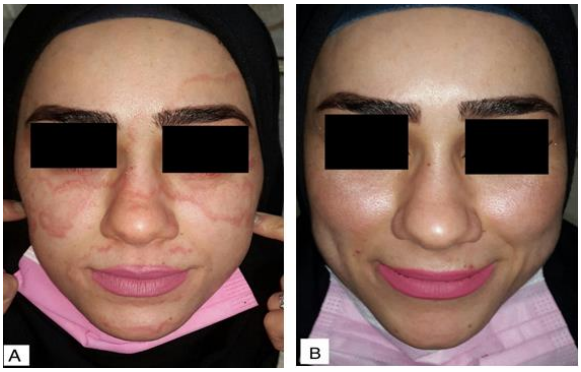

Figure 1 Twenty-four year old female with chronic tinea faciei involving the entire face, (A) before treatment and (B) four weeks after treatment.

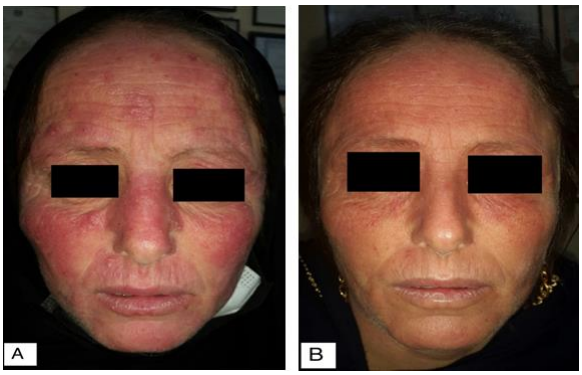

Figure 2 Fifty-two year old female with lupus erythematosus-like tinea faciei involving the entire face, (A) before treatment and (B) four weeks after treatment.

males and 150(37.5%) females with different kinds of dermatophytosis. The age of the patients ranged from 6-70 years with a mean of 30 years. Disease duration ranged from 6-32 months with a mean of 11 months. The number of familial house contact infections were varied but ranged from 1-12 with a mean of 5 cases.

All enrolled cases had chronic resistant or relapsing dermatophyte infections **(Figures 1a&2a)** and were received single therapy using oral fluconazole,itraconazole or griseofulvin and/ or topical antifungal creams like terbinafine, clotrimazole, miconazole and whitfeild ointment and this regimen frequently results in treatment failures and relapses especially when given in standard doses and for conventional period . Scrape for fungus in KOH examination was positive for all enrolled cases. Out of 92 samples, dermatophyte was recognized in 63 (68%) both by PCR and/ or culture for the 92 cases. PCR positive were 57 (90%) of 63 samples, culture positive was 43 of 63 samples. T. mentagrophytes/ T. interdigitale, 40 (40/63.63%, 26 by culture, 14 by PCR) was the most commonly isolated species.

Depending on the sequencing results, we could confirm that among 26 cultural isolated T. mentagrophytes species, surprisingly, 18 were T. mentagrophytes ITS type VIII (Indian type), 5 were T. mentagrophytes ITS type V (Iranian type), and 2 were anthropophilic T. interdigitale ITS type II. Seven (39%) out of 18 T.mentagrophytes ITS type VIII (Indian type) were terbinafine resistant.[6]

The clinical features of the dermatophytosis were as follow: tinea corporis was the dominant superficial fungal skin infection recorded in 142 (35.5%) of patients followed by tinea faciei 110 (27.5%), tinea manuum 70 (17.5%), tinea pedis 34 (8.5%), tinea cruris 30 (7.5%), and tinea barbae 14 (3.5%).

The response to the therapeutic regimen started after 5-7 days by decreasing in the redness, itching, inflammation, and scales. An obvious response was seen at the end of the two weeks while complete clearance at four weeks after starting treatment and obvious cure after 8weeks therapy **(Figures 1 & 2)**.

Regarding the percentage of the degree of response in each visit during treatment, were as follow:

Two weeks after starting treatment: 329 (82.25%) of the cases displayed moderate response and 71 (17.75%) showed marked response.

Four weeks after starting treatment (phase one): All patients showed marked and complete clearance of the lesions.

Eight weeks after starting treatment documented complete recovery and obvious cure in all treated patients (phase two).

Eight weeks follow up after stopping eight weeks therapy showed relapse rate in 8 (2%) patients.

This combination was well tolerated with no serious systemic or topical adverse effects were recorded apart from mild transient elevation in serum AST and ALT were seen in 10 (2.5%) of patients 4 weeks after starting treatment and in 9 (2.25%) patients 8 weeks after starting treatment that disappeared after discontinuation of treatment.

Discussion

It has been proposed that diverse mechanisms of action of different oral antifungals may provide synergistic effects leading to increment antifungal activity (i.e. combination of itraconazole/ terbinafine).[16-18] The use of an oral antifungals in combination with topical medication (terbinafine, ketoconazole, miconazole, selenium sulfide, etc.) may enhance the efficacy of these medications.

In the last years, emergence of massive cases of chronic or relapsing dermatophytosis has been observed worldwide including Iraq, so, the purpose of the combined multiple antifungal therapy as used in the present study is to get synergistic effect to overcome drug resistance and to decrease the relapsing rate.

Theoretically, ketoconazole and itraconazole inhibit 14-alpha-demethylase enzyme while terbinafine inhibits squalene epoxidase enzyme, so, the combination of antifugal treatment used in this study as two diverse regimens for 2 months, result in dual and sequential inhibition of fungal ergosterol synthesis.[19,20]

The combination of oral ketoconazole and terbinafine has not yet been established in the treatment of dermatophytosis and this is the first study that documented this combination in the treatment of chronic relapsing dermatophytosis with very encouraging therapeutic results.

Based on earlier studies, oral terbinafine or itraconazole in standard doses and duration is frequently considered as a first line therapy for dermatophytosis with changeable but considerable cure rates.[21-25]

A combination of oral antifungals (i.e. itraconazole and terbinafine) has been used recently in the management of dermatophytosis.[14]

A study in 1994, using daily terbinafine in a dose of 250mg daily for seven days for the management of tinea corporis and/ or tinea cruris was showed a clinical and mycological cure rate as high as 100%.[21] While in a recent study, only 35% mycological cure rate was achieved after 3 weeks of oral terbinafine therapy in a dosage of 250mg/day in tinea corporis or cruris.[14] This current decrease in the therapeutic efficacy is well confirmed by a tremendous increase in dermatophytosis cases seen by Iraqi dermatologists in daily clinical practice along with a failure to respond to the ordinary treatment for dermatophytosis. In the current work, a combination therapy showed 100% cure rate which is slightly higher than the reported cure rate by another study (90%) where terbinafine and itraconazole was used in combination[14] while much higher than other reports in which oral itraconazole and terbinafine was used as a monotherapy for the management of tinea cruris and corporis.[10,14,26]

The present study recorded the lowest recurrence rate (2%) at two months after the completion of therapy when compared to 57% two weeks after monotherapy with oral terbinafine 250 mg daily in tinea corporis or cruris[26] and to 11.2% failure rate following 3 weeks combination study of oral oral itraconazole 200 mg and terbinafine 250mg daily.[14] The cause of relapse of fungal infection in (2%) of patients, in the present work, could be attributed to treatment interruption by these patients or reinfection from another family member with active dermatophytic lesion rather than a real relapse.

In this work, tinea corporis was the dominant dermatophytosis recorded in 142 (35.5%) of patients followed by tinea faciei 110 (27.5%), tinea manuum 70 (17.5%), tinea pedis 34 (8.5%), tinea cruris 30 (7.5%), and tinea barbae 14 (3.5%). These results were comparable to other published literature where tinea corporis was the most prevalent clinical types.[27-29]

Sharing of personal hygiene equipment and overcrowding could be a possible cause of the increased propagation of tinea corporis, and tinea faciei.[3] While the epidemic status in Iraqi population could be explained by harsh living in Camps as results of prolonged wars situations, poor housing, bad social status and difficult livings, in addition to other well recognized factors.

In the current work, T. mentagrophytes/ T. interdigitale, was the most common cultural isolated species observed in 63% of patients. While these results in agreement with many initial literatures where T. mentagrophytes was the most frequent isolated from the specimens,[30,31] it differed with many preceding studies in which M. canis was the dominant responsible species of dermatophytosis[32,33] while another report[34] observed that T. rubrum was the dominant responsible species.

In the present work, all cases showed complete clinical clearance of the skin lesions one month after starting treatment but the treatment has been continued for another month using different regimen aiming to eliminate any responsible microscopic pathogens that could be a cause for recurrence of the lesion. The cause of this chronic or relapsing dermatophytosis is not well known but we can assume that many of these patients were misdiagnosed for other cutaneous diseases such as eczema, psoriasis, photosensitivity, and others with improper treatment by topical or systemic steroids.[3] Another explanation is the emergence of new resistant strain among Iraqi patients called T. mentagrophytes type VIII[6] with its chronic nature and more ease spread. In addition, relapsing dermatophyte infections could be due to infection transmission from symptom-free carriers like family members and pets especially in overcrowded families causing interfamily spread and reinfection despite initial cure. Also, sharing of infected footwear, clothings, towels, and bedding may contribute to the reinfection and relapse after initial cure.

This study also documented that combination of drugs was well tolerated with no serious systemic or topical adverse effects were recorded apart from mild transient elevation in serum AST and ALT were seen in 10 (2.5%) of patients 4 weeks after starting treatment and in 9 (2.25%) patients 8 weeks after starting treatment that disappeared after discontinuation of treatment but no features of real hepatitis.

The combination of different classes of antifingal therapy with different mechanism of action used in this study was observed to be as safe as monotherapy treatment. This observation is consistent with earlier studies[13,14] where a combination of itraconazole and terbinafine for

3 weeks duration in the same doses of the present study was reported to be safe with no serious toxic side effects.[14] In the another study, a higher doses (itraconazole 200-400 mg/day and terbinafine 250-1000 mg/day) for 2-7 months was found to be safe in the patients of chromoblastomycosis.[13] Both of these studies support the safety profile of the our new therapeutic regimen.

Conclusion

This new therapeutic multiple combination is effective in all included types of dermatophytosis especially with chronic and relapsing course of the disease. This combination showed a very high cure rate with a very low recurrence rate. Also, this new therapy regimen is well tolerated and does not seem to have remarkable side effects. So, this combined multiple drugs regimen used in this study could provide an alternative for patients with chronic or relapsing dermatophytosis who failed to respond to standard treatment and it seems to have promising results in the management of these difficult fungal infections.

References

1. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. *Mycoses*. 2008;**51**:2–15.
2. Ajello L. Geographic distribution and prevalence of the dermatophytes. *Ann N Y Acad Sci*. 2006;**89**:30-8.
3. Sharquie K E, Jabbar R I. Major outbreak of dermatophyte infections leading into imitation of different skin diseases: trichophyton mentagrophytes is the main criminal fungus. *J Turk Acad Dermatol*. 2021;**15(4)**:91-100.
4. Taghipour S, Shamsizadeh F, Pchelin IM, Rezaei-Matehhkolaei A, Zarei Mahmoudabadi A, Valadan R, *et al*. Emergence of terbinafine resistant trichophyton mentagrophytes in Iran, harboring mutations in the squalene epoxidase (SQLE) gene. *Infect Drug Resist*. 2020;**13**:845-50.
5. Verma S, Madhu R. The great Indian epidemic of superficial dermatophytosis: an appraisal. *Indian J Dermatol*. 2017;**62**:227-36.
6. Uhrlass S, Alhilaifawi AFH, Sharquie KE, Alhamami HR, Al-Qahar GHA, Tabra MKH, *et al*. Dermatophyte survey from Baghdad, Iraq – emergence of terbinafine resistant Trichophyton mentagrophytes Type VIII India. Submitted (MAY- 2020) to the EMBL/GenBank/DDBJ databases.
7. Nenoff P, Verma SB, Ebert A, Süß A, Fischer E, Auerswald E, *et al*. Spread of terbinafine-resistant Trichophyton mentagrophytes Type VIII (India) in Germany-"The Tip of the Iceberg?". *J Fungi (Basel)*. 2020;**6**:207.
8. Verma, S.B. Comment on: Emergence of recalcitrant dermatophytosis in India. *Lancet Infect Dis*. 2018;**18**:718–9.
9. Bishnoi A, Vinay K, Dogra S. Emergence of recalcitrant dermatophytosis in India. *Lancet Infect Dis*. 2018;**18**:250–1.
10. De Doncker P, Pande S, Richarz U, Garodia N. Itraconazole: What clinicians should know? *Indian J Drugs Dermatol*. 2017;**3**:4-10.
11. Panda S, Verma S. The menace of dermatophytosis in India: The evidence that we need. *Indian J Dermatol Venereol Leprol*. 2017;**83**:281-4.
12. Johnson MD, MacDougall C, Ostrosky-Zeichner L, Perfect JR, Rex JH. Combination antifungal therapy. *Antimicrob Agents Chemother*. 2004;**48**:693-715.
13. Gupta AK, Taborda PR, Sanzovo AD. Alternate week and combination itraconazole and terbinafine therapy for chromoblastomycosis caused by Fonsecaea pedrosoi in Brazil. *Med Mycol*. 2002;**40**:529-34.
14. Sharma P, Bhalla M, Thami GP, Chander J. Evaluation of efficacy and safety of oral terbinafine and itraconazole combination therapy in the management of dermatophytosis. *J Dermatolog Treat*. 2020;**31(7)**:749-53.
15. Sharquie K E, Noaimi A A, and Al-Salam W S. The safety of oral ketoconazole in the treatment of skin diseases (Single blinded, therapeutic, comparative study). J Cosmet Dermatol Sci Appl.2018;**8**:264-71.
16. Baran R, Kaoukhov A. Topical antifungal drugs for the treatment of onychomycosis:

an overview of current strategies for monotherapy and combination therapy. *J Eur Acad Dermatol Venereol*. 2005;**19**:21-9.
17. Olafsson JH, Sigurgeirsson B, Baran R. Combination therapy for onychomycosis. *Br J Dermatol*. 2003;**149(65)**:15–8.
18. Evans EGV. Drug synergies and the potential for combination therapy in onychomycosis. *Br J Dermatol*. 2003;**149(65)**:11–3.
19. Ghannoum MA, Rice LB. Antifungal agents: mode of action, mechanisms of resistance, and correlation of these mechanisms with bacterial resistance. *Clin Microbiol Rev*. 1999;**12**:501-17.
20. Eil C. Ketoconazole binds to the human androgen receptor. Horm Metab Res. 1992; **24**:367-70.
21. Farag A, Taha M, Halim S. One-week therapy with oral terbinafine in cases of tinea cruris/ corporis. *Br J Dermatol*. 1994;**131**:684-6.
22. Noppakun N, Phuphaibool K. Treatment of dermatophytosis with new systemic antifungal agent, itraconazole. *J Med Assoc Thai*. 1992;**75**:99-103.
23. Acharya KM, Mukhopadhyay A, Thakur RK, Mehta T, Bhuptani N, Patel R. Itraconazole versus griseofulvinin the treatment of tinea corporis and tinea cruris. *Indian J Dermatol Venereol Leprol*. 1995;**61**:209-11.
24. De Keyser P, De Backer M, Massart DL, Westelinck KJ. Two-week oral treatment of tinea pedis, comparing terbinafine (250 mg/day) with itraconazole (100 mg/day): a double-blind, multicentre study. *Br J Dermatol*. 1994;**130**:22-5.
25. Bourlond A, Lachapelle JM, Aussems J, Boyden B, Campaert H, Conincx S, *et al*. Double-blind comparison of itraconazole with griseofulvin in the treatment of tinea corporis and tinea cruris. *Int J Dermatol*. 1989;**28**:410-2.
26. Majid I, Sheikh G, Kanth F, Hakak R. Relapse after oral terbinafine therapy in dermatophytosis: A clinical and mycological study. *Indian J Dermatol*. 2016;**61**:529-33.
27. Ellabib MS,Khalifa Z,Kavanagh K.Dermatophytes and other fungi associated with skin mycoses in Tripoli, Libya. *Mycoses*. 2002;**45**:101-4.
28. Mahmoud AL. A study of dermatophytoses in Sana'a, Yemen Republic. *Mycoses*. 2002;**45**:105-8.
29. Lange M, Nowicki R, Barańska-Rybak W, Bykowska B. Dermatophytosis in children and adolescents in Gdansk, Poland. *Mycoses*. 2004;**47**:326-9.
30. Sowmya N, Appalaraju B, Surendran P, Srinivas CR. Isolation, identification and comparatative analysis of SDA and DTM for dermatophytes from clinical samples in a tertiary care hospital. *IOSR J Dent Med Sci*. 2014;**13**:68-73.
31. Rashidian S, Falahati M, Kordbacheh P, Mahmoudi M, Safara M, Sadeghi Tafti H, *et al*. A study on etiologic agents and clinical manifestations of dermatophytosis in Yazd, Iran. *Curr Med Mycol*. 2015;**1**:20-5.
32. Atzori L, Pau M, Aste N, Aste N. Dermatophyte infections mimicking other skin diseases: a 154-person case survey of tinea atypica in the district of Cagliari (Italy). *Int J Dermatol*. 2012;**51**:410-5.
33. Sharquie KE, Al Ani SM, Ali TM. Microsporum canis epidemic in Iraq children. Journal of the Faculty of Medicine-Baghdad. 1992;34:95-99.
34. Mohammed SJ, Noaimi AA, Sharquie KE. A survey of dermatophytes isolated from Iraqi patients in Baghdad city. *AL-Qadisiya Medical Journal*. 2015;**11**:10-15.