Actas Dermosifiliogr. 2012;103(9):778–783

ACTAS Dermo-Sifiliográficas

Full English text available at www.elsevier.es/ad

REVIEW ARTICLE

Update on the Treatment of Superficial Mycoses☆

M. Pereiro Ferreirós Jr.,* F.J. García-Martínez, J. Alonso-González

Departamento de Dermatología, Complejo Hospitalario Universitario, Facultad de Medicina, Universidad de Santiago de Compostela, La Coruña, Spain

Received 28 July 2011; accepted 15 January 2012
Available online 23 October 2012

KEYWORDS
Superficial mycoses;
Dermatophytoses;
Candidiasis;
Therapies;
Antifungal agents

Abstract We review the current treatments available for superficial mycoses and discuss recent developments in pharmacotherapy and the most useful adjuvant treatments. Special emphasis is placed on the proper use of conventional therapies and a number of pharmacoeconomic issues. The review also offers an update on the best treatment choices in particular circumstances. Finally, we discuss some novel contributions found in the literature.

PALABRAS CLAVE
Micosis superficiales;
Dermatofitosis;
Candidiasis;
Terapéutica;
Antifúngicos

Actualización en el tratamiento de las micosis cutáneas

Resumen Se revisa la terapéutica disponible actualmente para el tratamiento de las micosis superficiales, las novedades existentes en el campo de la quimioterapia y los tratamientos coadyuvantes más útiles en este terreno. Se hace especial hincapié en el adecuado uso de los tratamientos convencionales y en algunos aspectos farmacoeconómicos relacionados con el tema. Se actualizan los procedimientos terapéuticos más adecuados en circunstancias especiales. Finalmente, se discuten algunas aportaciones novedosas encontradas en la literatura revisada.

Introduction

Treatment review articles usually focus on recently investigated drugs. However, these new drugs are sometimes of little use in routine clinical practice because they are not first-line options. In Spain, as in the rest of Europe, the most common mycoses are pityriasis versicolor,[1] the various clinical forms of dermatophytosis,[2–4] and candidiasis. In this review of current treatments, we focus on these 3 groups of mycoses and their first-line treatments.

Our aim is to answer several questions: Are any new treatments available for superficial mycoses? Are new treatments needed, or are the conventional treatments adequate? And finally, do we make good use of the available resources, or do we need to be more efficient in our treatment of superficial mycoses?

What is needed, we believe, is not merely a list of recently developed treatments but a review of ways to

☆ Please cite this article as: Pereiro Ferreirós Jr M, et al. Actualización en el tratamiento de las micosis cutáneas. Actas Dermosifiliogr. 2012;103:778-83.

* Corresonding author.
E-mail address: manuel.pereiro.ferreiros@usc.es (M. Pereiro Ferreirós Jr.).

1578-2190/$ - see front matter

improve clinical outcomes through the proper use of conventional drugs. We also believe that costs can be reduced without sacrificing outcome quality.

We draw on our personal experience as well as evidence from 3 types of publications: experimental research, clinical trials, and pharmacoeconomic studies.

In routine clinical practice, the treatment of superficial mycoses with antifungals differs from that of infections treated with antibiotic therapy in that susceptibility testing is only useful in infections caused by *Candida* organisms.[5,6] In the case of other yeasts, such as *Malassezia*[7] and dermatophytes,[8] susceptibility tests are difficult to perform, poorly standardized, and purely of academic interest.

Available Treatments Are Well Known But Poorly Used

Since the appearance of griseofulvin and the polyenes in the 1950s, the pharmacopeia for superficial mycoses has seen the addition of topical treatments, such as the azoles, ciclopirox, and amorolfine as well as the oral triazoles and allylamines. Around 60 new antifungal substances are currently being investigated. These include new formulations and semisynthetic derivatives of polyenes and amphotericin, new peptides such as echinocandins and aerothricines, and novel substances such as amino acids, sordarins, macrolides, terpenes, saponins, and flavans.[9,10] Although many of these drugs have been tested against dermatophytes in the laboratory, the specialized products that have been brought to market are expensive and are not indicated for superficial mycoses, except in extreme cases or in a hypothetical future.[11]

Moreover, despite the large number of clinical trials of antifungal agents conducted over recent decades, we found that the meta-analyses on this topic include a strikingly small number of trials, suggesting a lack of homogeneity in the methodologies used.[12–14] Review articles on this subject therefore invariably conclude by indicating that further studies are needed in the field of superficial mycoses.[15]

How Much Is Being Spent on Antifungal Agents in Spain?

A similar situation can be seen in pharmacoeconomic studies on antifungal agents. The results of these studies vary greatly depending on their objectives (cost-effectiveness, cost-utility, cost-benefit), the sponsoring institution (public body or private company), time frame and geographic scope, type of cost evaluated (only the drug or the entire medical intervention), and outcome (cure or disease-free days).[16] Pharmacoeconomic studies identify, one way or another, the least expensive treatment, but they do not clearly demonstrate the importance of choosing the least expensive option.[17]

We requested data from the Spanish Ministry of Health for 2001, a year in which a complete census of Spain's population was conducted (Table 1). According to the data provided, 1 package of topical antifungal agent was used for every 4 people and 1 package of oral antifungal agent was used for every 24 people in the country in 2001. Although a more in-depth analysis is warranted,[17] these data clearly suggest that antifungal agents are being overused in Spain.

Table 1 Estimated Expenditure in Spain on Topical and Systemic Antifungal Agents, Based on Spanish Ministry of Health and Consumer Affairs Data From 2001 Provided in 2007[a].

Topical	
10 800 000 units[b]	€36 060 726.26
Gynecological	
2 400 000 units	€8 155.74
Systemic	
1 700 000 units[c]	€24 636 920.42
Fluconazole	€9 524 603
Itraconazole	€8 429 519
Terbinafine	€6 682 798

[a] Official population of Spain (2001 census): 40 847 371.
[b] One package of topical antifungal agent for every 4 inhabitants.
[c] One package of systemic antifungal agent for every 24 inhabitants.

Recent studies of superficial mycoses have focused primarily on the best use of known resources,[18] and on the search for efficacy enhancers, such as adjuvant therapies, for both topical and oral treatments.[19,20]

First-Line Treatments and Practical Aspects

Griseofulvin

For more than 40 years, griseofulvin has been the first-line treatment for ringworm of the scalp in pediatric patients (Table 2).[21–23] In that setting, griseofulvin is more effective than fluconazole and just as effective as itraconazole and terbinafine[24] but much less expensive. The rate of adverse effects associated with griseofulvin is low and does not increase at high doses (15-20 mg/kg/d in children).[20,21] Current guidelines recommend continuing griseofulvin treatment for at least 6 weeks at a dose adjusted to body weight: in children weighing < 10 kg, the dose should not exceed 250 mg/d; in patients weighing 10 to 20 kg, the recommended dose is 375 mg/d; in patients weighing 20 to 40 kg, 500 mg/d; and in patients weighing > 40 kg, 1000 mg/d. Because the half-life of the drug is less than 24 hours, the guidelines recommend administering the daily dose in 2 doses.[20,21]

Imported cases of ringworm caused by *Trichophyton tonsurans* may be resistant to griseofulvin and require treatment with terbinafine. The likelihood of adverse reactions is very low and this possibility should only be taken into consideration in patients with a history of serious adverse reactions to other drugs.[14]

The efficacy of griseofulvin can be improved significantly by the simultaneous ingestion of fatty foods, which stabilize the gastric pH, and by the application of fomentations because local heat and moisture cause sweating, which in turn enhances the transcutaneous excretion of the drug.[21]

Table 2 First-Line Treatments and Adjuvant Therapies.

Clinical Presentation	First-Line Treatment	Second-Line Treatment	Adjuvant Treatment
Tinea			
Pedis	Topical terbinafine	Topical ciclopirox. Topical or oral itraconazole or terbinafine	Fomentations Hand or foot baths Occlusive dressing
Cruris	Topical azole		
Corporis	Topical azole		
Barbae	Griseofulvin		Imidazole shampoo, fomentations, pH monitoring
Capitis	Griseofulvin		
Extensive tineas and tineas affecting the glabrous skin of the hands	Oral terbinafine	Oral itraconazole	Topical azole
Inflammatory tineas[a]	Topical azole	Topical terbinafine or ciclopirox	Occlusive dressing combined with topical corticosteroids
Onychomycosis	Switch therapy: topical ciclopirox, oral itraconazole, oral terbinafine	Switch therapy: oral itraconazole, oral terbinafine, topical ciclopirox	Nail avulsion Photodynamic therapy
Pityriasis versicolor			
Extensive	Oral itraconazole	Topical terbinafine or ciclopirox	Imidazole gel, before oral treatment and/or as maintenance therapy
Localized	Topical azole		
Oropharyngeal candidiasis	Nystatin (polyenes) for mild forms	Fluconazole for resistant or recurrent forms	Oral rinse containing bicarbonate/chlorhexidine

[a] Inflammatory tineas not belonging to any other category that do not require systemic treatment.

Oral Triazoles

Fluconazole is the first-line treatment for recurrent cases of oropharyngeal and genital candidiasis[25] that respond poorly to topical treatments, and for severe subcutaneous and systemic mycoses (Table 2).[26,27] It is the third-line treatment for tinea infections that affect terminal hair and/or the nails (onychomycosis) in adults. Failed candidiasis treatments are more often associated with incorrect administration than with resistance.[18,19] The treatment of candidiasis should always be accompanied by dietary and hygiene measures, ranging from conventional iron metabolism monitoring to changes in eating habits.[25,28] Itraconazole could be considered the German Shepherd of oral antifungal agents because it is second-best at nearly everything. It is better than terbinafine, though not as effective as griseofulvin, in the treatment of mycoses caused by *Microsporum canis*. It is the first-line monotherapy for extensive pityriasis versicolor (Table 2). Itraconazole is also used to reduce the cost of switch therapy for onychomycosis, as will be explained below (Table 3). The pharmacokinetic problems of itraconazole will probably be improved in the new formulation that is currently being tested.[29,30]

Topical Azoles

The topical azoles are a large, well-known group of substances to which new products are continually being added.

Table 3 Switch Therapy for Onychomycosis: Comparison of Net Cost Per 500 000 Patients[a].

Least Expensive	Most Expensive
Ciclopirox or amorolfine, 1 mo	Continuous oral itraconazole, 3 mo
Followed by: oral itraconazole pulse therapy, 3 mo	Followed by: continuous oral terbinafine, 3 mo
Followed by: continuous oral terbinafine, 3 mo	Followed by: topical ciclopirox or amorolfine, 3 mo
Cost for 500 000 patients: €2 091 508	Cost for 500 000 patients: €5 837 400
Response rate: 97.9%[b]	Response rate: 96.2%[b]

[a] The options compared are the 2 switch therapy regimens with the highest response rates.
[b] The computer model took into account the response rate for each of the medications used.

Topical azole treatments are cheap, potent, and broad-spectrum, with activity against dermatophytes, molds, and yeasts (Table 2). The absorption and, therefore, the effectiveness of topical azoles can be increased with the application of occlusive dressings. The use of topical azoles in combination with topical corticosteroids has been recommended in the treatment of inflammatory tineas. The addition of a topical corticosteroid enhances efficacy by

decreasing the inflammatory component, facilitating the restoration of the skin's barrier function and normal flora, and diminishing the Herxheimer reaction that sometimes occurs at the start of treatment.[31] This combination should not be used to treat tineas caused by anthropophilic fungi because in such cases it can lead to the development of tinea incognito and Majocchi granulomas.[18]

Allylamines

In adults, single-drug therapy with oral terbinafine is the first-line treatment for onychomycosis and extensive tineas that respond poorly to topical treatment (Table 2). In children, the use of oral terbinafine is limited to patients over 2 years of age with griseofulvin-resistant cases of *T tonsurans*. A regimen of 6 weeks is recommended for infections of the scalp or fingernails and of 12 weeks for onychomycosis of the toenails. The recommended regimen in the United States, which is based on the availability of scored 125 mg tablets, calls for *a)* half a tablet daily for children weighing under 20 kg, *b)* 1 tablet daily for children weighing 20 to 40 kg, and *c)* 1 tablet twice daily for children weighing over 40 kg.[20]

In Spain, oral terbinafine is sold in scored 250 mg tablets and cannot therefore be prescribed to children weighing under 20 kg.[14,20,24] The role of oral terbinafine in switch therapy for onychomycosis is discussed below.

Topical terbinafine is the topical antifungal agent most effective against tinea pedis in young adults (Table 2); however, because it is more expensive than azoles, this drug has been relegated to the role of a rescue medication.[32–34]

Concerns regarding resistance in cases of *M canis* infection are inconsequential because infections caused by this microorganism tend to respond very well to griseofulvin.[18]

Morpholines and Ciclopirox

Morpholines and ciclopirox are highly potent broad-spectrum drugs capable of penetrating both glabrous skin and nail plates. They are effective as monotherapy against white superficial onychomycosis and athlete's foot in older patients who are already taking multiple medications. They are also useful in switch therapy (Table 2). There have been reports of irritant reactions to these drugs, although most of these have been associated with excipients.[35]

Polyenes (Nystatin)

Nystatin is highly effective against candidiasis of both the skin and the mucous membranes, even in cases that are resistant to fluconazole and all other azoles.[36] Because of its good safety profile and the fact that most patients tolerate it well, nystatin is recommended for prolonged treatment (Table 2). In the United States, there have been reports of contact dermatitis associated with the topical excipients used in certain generic preparations.[20]

Recommendations for Reducing the Duration of Oral Treatment

Like the use of occlusive dressings, mentioned above, the use of switch therapy can significantly reduce the duration of systemic antifungal treatment. Switch therapy is particularly useful in elderly, immunodeficient, or polymedicated patients with onychomycosis or extensive mycosis of the terminal hair or glabrous skin. In switch therapy, topical antifungal treatment is initiated prior to the start of oral treatment.[13,18–20,29]

In patients with onychomycosis, the following procedure is recommended. Specimens should be obtained for direct examination and culture and a topical antifungal lacquer, to be applied once daily for 1 month, should be prescribed. After 1 month, depending on the results of the direct examination and culture, oral treatment may be initiated. Topical treatment should be enhanced by using fomentations or hand or foot baths to increase the permeability of the nail plate.[29,30,37,38]

The use of imidazole shampoo for at least 15 days prior to the start of a 7-day regimen of oral itraconazole can be effective against mycoses affecting hair-bearing areas as well as extensive pityriasis versicolor.[20]

In ringworm of the scalp, griseofulvin should be used at high doses for 6 weeks. The response rate increases considerably with the addition of fomentations and topical imidazole in a cream, solution, or shampoo.[20,24] Noninflammatory trichophytic tineas in adults are treated with a continuous 1-month regimen of oral terbinafine plus the topical treatment described above (Table 2).[24]

Cost-Effectiveness in Specific Situations

The most effective topical monotherapies for tineas, inflammatory or not, affecting hairless, glabrous, and inguinal skin in young adults are terbinafine and ciclopirox, while the least expensive are tolnaftate and undecylenic acid, both available in various presentations. However, we believe that topical azoles should be the first-line treatment because their efficacy is similar to that of terbinafine and ciclopirox but they are less expensive (Table 2). In order to increase drug penetration and effectiveness, shorten treatment duration, and prevent recurrence, the use of occlusive dressings, fomentations, and hand and foot baths is essential.[20]

As noted above, combination therapy with an azole and a topical corticosteroid is especially useful at the start of treatment against inflammatory ringworm, in the event of a Herxheimer reaction,[31] and in patients who, on completion of treatment, present eczematous or irritative symptoms.[20]

Switch Therapy in Onychomycosis

Switch therapy is the first-line treatment approach in onychomycosis.[9,13] The drugs used in a switch therapy regimen can be administered in different sequences, with little impact on the final efficacy but large variations in cost. It is important to focus not on the cost of treating a single patient but on the expenditure of a large group of doctors over many years. Table 3 shows the final cost for 500 000

patients of 2 regimens of similar efficacy, 1 significantly less expensive than the other.[39]

Another approach that reduces the cost of treating onychomycosis is oral pulse therapy, a method first used in the 1960s with griseofulvin.[40,41] At present, pulse therapy with terbinafine is considered to be similar to continuous therapy in terms of efficacy and safety. The recommended regimens range from 500 mg daily for the first week of each month for 3 months[42] to 500 mg daily for the first and third months of a 3-month regimen.[43]

Various topical response enhancers aimed at reducing the need for oral therapy in onychomycosis have been proposed.[30] This group includes substances that enhance the penetration of the topical treatment into the nail, such as urea, urea hydrogen peroxide, salicylic acid, thioglycolic acid, acetylcysteine, 2-mercaptoethanol, 2-nonyl-1,3-dioxolane, keratinases, and phosphoric acid.[29] Other methods used to increase nail penetration include abrasion of the nail surface by mechanical means or low-powered laser, total nail avulsion by laser, and conventional surgical avulsion.[29,44]

Recent studies have found no association between surgical avulsion and subsequent problems with nail regrowth, and no differences between total and partial avulsion.[38,44] Outcomes improved, however, when surgical avulsion was accompanied by topical occlusive treatment until the nail had regrown completely. Overall, surgical avulsion was found to have similar efficacy to, and no advantage over, medical treatments.[38,44]

One of the most promising treatment options is photodynamic therapy. This technique is effective against mucocutaneous candidiasis,[45–47] onychomycosis caused by *Trichophyton rubrum*,[48–51] and extensive folliculitis caused by *Pityrosporon* organisms.[52] The results of photodynamic therapy have, however, been less promising in cases of tinea cruris.[53] We therefore believe that further studies are needed to determine dosages and treatment regimens.

Other alternatives for treating onychomycosis, such as boosted treatments[54,55] and iontophoresis, are still in the experimental stage.[56,57]

Conclusion

In summary, we consider that the expenditure on topical and systemic antifungal agents in Spain is very high. Moreover, we believe that, in most cases, the proper use of conventional drugs makes the use of more expensive drugs unnecessary. In the case of onychomycosis, we believe that the use of the recommended switch therapy could lead to considerable savings.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Crespo-Erchiga V, Gómez-Moyano E, Crespo M. La pitiriasis versicolor y las levaduras del género *Malassezia*. Actas Dermosifiliogr. 2008;99:764–71.
2. Pereiro Miguens M, Pereiro E, Pereiro Jr M, Pereiro-Ferreirós MM, Toribio J. Incidencia de los dermatofitos en España desde 1926 a 1994. Actas Dermosifiliogr. 1996;87:77–84.
3. Ameen M. Epidemiology of superficial fungal infections. Clin Dermatol. 2010;28:197–201.
4. Seebacher C, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. Mycopathologia. 2008;166:335–52.
5. Carrillo Muñoz A, Quindós G, Arevalo MP, Bornay F, Cabañes FJ, Casals JB, et al. Aportaciones del comité de la AEM para la estandarización de pruebas de estudio de la sensibilidad *in vitro* a los antifúngicos: Método de difusión en disco. Rev Iberoam Micol. 1996;13:S101–4.
6. Quindós G, Abarca L, Carrillo A, Arévalo P, Bornay FJ, Casals JB, et al. Multicenter survey of in vitro antifungal resistance in yeasts of medical importance isolated from Spanish patients. Rev Iberoam Micol. 1999;16:97–100.
7. Garau M, Pereiro Jr M, Palacio A. In vitro susceptibilities of *Malassezia* species to a new triazole, albaconazole (UR-9825), and other antifungal compounds. Antimicrob Agent Chemother. 2003;47:2342–4.
8. Fernández-Torres B, Pereiro Jr M, Guarro J. Comparison of two methods for antifungal susceptibility testing of Trichophyton rubrum. Eur J Clin Microbiol Infect Dis. 2002;21:70–1.
9. Kumar S, Kimballt AB. New antifungal therapies for the treatment of onychomycosis. Expert Opin Investig Drugs. 2009;18:721–34.
10. Di Santo R. Natural products as antifungal agents against clinically relevant pathogens. Nat Prod Rep. 2010;27:1084–98.
11. Silva-Lizama E. Antifúngicos del futuro. Med Cut Iber Lat Am. 2004;32:229–30.
12. Hart R, Bell-Syer SEM, Crawford F, Torgerson DJ, Young P, Russell I. Systematic review of topical treatments for fungal infections of the skin and nails of the feet. BMJ. 1999;319:79–82.
13. Gupta AK, Ryder JE, Johnson AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. Br J Dermatol. 2004;150:537–44.
14. Tey HL, Tan AS, Chan YC. Meta-analysis of randomized, controlled trials comparing griseofulvin and terbinafine in the treatment of tinea capitis. J Am Acad Dermatol. 2011;64:663–70.
15. Carrillo-Muñoz AJ, Tur-Tur C, Hernández-Molina JM, Santos P, Cárdenes D, Giusiano G. Antifúngicos disponibles para el tratamiento de las micosis ungueales. Rev Iberoam Micol. 2010;27:49–56.
16. Arenas-Guzmán R, Tosti A, Hay R, Haneke E. Pharmacoeconomics – an aid to better decision-making. JEADV. 2005;19:34–9.
17. Pereiro Ferreirós M. Coste-eficacia en el tratamiento de las micosis cutáneas. XIX Reunión Clínica Internacional de Dermatología de Barcelona (28 February-1 March 2008). Barcelona; 2008.
18. Baran R, Hay RJ, Garduno JI. Review of antifungal therapy, part II: Treatment rationale, including specific patient populations. J Dermatol Treat. 2008;19:168–75.
19. Yang W, Wiederhold NP, Williams RO. Drug delivery strategies for improved azole antifungal action. Expert Opin Drug Deliv. 2008;5:1199–216.
20. Millikan LE. Current concepts in systemic and topical therapy for superficial mycoses. Clin Dermatol. 2010;28:212–6.
21. Develoux M. Griseofulvin. Ann Dermatol Venereol. 2001;128:1317–25.
22. Monteagudo B, Pereiro Jr M, Peteiro C, Toribio J. Tinea capitis en el área sanitaria de Santiago de Compostela. Actas Dermosifiliogr. 2003;94:598–602.
23. Gómez Vázquez M, Sánchez-Aguilar D, Pereiro Jr M, Toribio J. Tiña inflamatoria de la ingle en una mujer por *T. mentagrophytes* var. *interdigitale*. Actas Dermosifiliogr. 2002;93:461–3.

24. González U, Seaton T, Bergus G, Jacobson J, Martínez-Monzón C. Systemic antifungal therapy for tinea capitis in children. Cochrane Database Syst Rev. 2007;17:C D004685.
25. Ramírez-Santos A, Pereiro Jr M, Toribio J. Vulvovaginitis de repetición. Valoración diagnóstica y manejo terapéutico. Actas Dermosifiliogr. 2008;99:190–8.
26. Pereiro Jr M, Labandeira J, Toribio J. Plantar hyperkeratosis due to Fusarium verticillioides in a patient with malignancy. Clin Exp Dermatol. 1999;24:175–8.
27. Pereiro Jr M, Abalde MT, Zulaica A, Caeiro JL, Flórez A, Peteiro C, et al. Chronic infection due to Fusarium oxysporum mimicking lupus vulgaris: Case report and review of cutaneous involvement in fusariosis. Acta Derm Venereol. 2001;81:51–3.
28. Runeman B, Rybo G, Forsgren-Brusk U, Larkö O, Larsson P, Faergemann J. The vulvar skin microenvironment: Impact of tight-fitting underwear on microclimate, pH and microflora. Acta Derm Venereol. 2005;85:118–22.
29. Browna MB, Khengarc RH, Turnerb RB, Forbesc B, Traynora MJ, Evans CRG, et al. Overcoming the nail barrier: A systematic investigation of ungual chemical penetration enhancement. Int J Pharmaceutic. 2009;370:61–7.
30. Elkeeb R, AliKhanb A, Elkeebc L, Huia X, Maibacha HT. Transungual drug delivery: Current status. Int J Pharmaceutic. 2010;384:1–8.
31. Havlickova B, Friedrich M. The advantages of topical combination therapy in the treatment of inflammatory dermatomycoses. Mycoses. 2008;51:16–26.
32. Evans EGV. Tinea pedis: clinical experience and efficacy of short treatment. Dermatology. 1997;194:3–6.
33. Monteagudo B, Pereiro Ferreirós Jr M, Fernández-Redondo V, Toribio J. Tinea pedis causada por *Trichophyton violaceum*. Actas Dermosifiliogr. 2002;93:35–7.
34. Sánchez-Schmidt M, Giménez-Jovani S, Peyrí-Rey J. Estudio de satisfacción con el tratamiento de las micosis en extremidades con terbinafina (SETTA). Actas Dermosifiliogr. 2005;96:285–90.
35. de Pádua CA, Uter W, Geier J, Schnuch A, Effendy I. German Contact Dermatitis Research Group (DKG); Information Network of Departments of Dermatology (IVDK). Contact allergy to topical antifungal agents. Allergy. 2008;63:946–7.
36. González-Vilas D, Pereiro Jr M. Candidiasis mucocutáneas. Piel. 2008;23:464–74.
37. Gunt HB, Kasting GB. Effect of hydration on the permeation of ketoconazole through human nail plate in vitro. Eur J Pharm Sci. 2007;32:254–60.
38. Malay DS, Yi S, Borowsky P, Downey MS, Mlodzienski AJ. Efficacy of debridement alone versus debridement combined with topical antifungal nail lacquer for the treatment of pedal onychomycosis: a randomized, controlled trial. J Foot Ank Surg. 2009;48:294–308.
39. Frankum LE, Nightengale B, Russo CL, Sarnes M. Pharmacoeconomic analysis of sequential treatment pathways in the treatment of onychomycosis. Managed Care Interface. 2005;18:55–63.
40. Reisner RM, Homer RS, Newcomer V, Sternberg TH. Onychomycosis of the feet: treatment with griseofulvin. Calif Med. 1960;93:217–23.
41. Seebacher C. Kontinuierliche oder diskontinuierliche Therapie der Onychomykosen mit resorptionsaktivem Griseofulvin? Mykosen. 1966;9:126–9.
42. Takahata Y, Hiruma M, Shiraki Y, Tokuhisa Y, Sugita T, Muto M. Treatment of dermatophyte onychomycosis with three pulses of terbinafine (500 mg day) 1 for a week. Mycoses. 2009;52:72–6.
43. Gupta AK, Lynch LE, Kogan N, Cooper EA. The use of an intermittent terbinafine regimen for the treatment of dermatophyte toenail onychomycosis. J Eur Acad Dermatol Venereol. 2009;23:256–62.
44. Grover C, Bansal S, Nanda S, Reddy BSN, Kumar V. Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. Br J Dermatol. 2007;157:364–8.
45. Souza R, Campos Junqueira J, Rossoni RD, Pereira CA, Munin E, Jorge AOC. Comparison of the photodynamic fungicidal efficacy of methylene blue, toluidine blue, malachite green and low-power laser irradiation alone against *Candida albicans*. Lasers Med Sci. 2010;25:385–9.
46. Bliss JM, Bigelow CE, Foster TH, Haidaris CG. Susceptibility of Candida species to photodynamic effects of Photofrin. Antimicrob Agent Chemother. 2004;48:2000–6.
47. García de Oliveira Mima E, Cláudia Pavarina A, Nordi Dovigo L, Vergani CE, Souza Costa CA, Kurachi C, et al. Susceptibility of *Candida albicans* to photodynamic therapy in a murine model of oral candidosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;109:392–401.
48. Watanabe D, Kawamura C, Masuda Y, Akita Y, Tamada Y, Matsumoto Y. Successful treatment of toenail onychomycosis with photodynamic therapy. Arch Dermatol. 2008;144:19–21.
49. Piraccini BM, Rech G, Tosti A. Photodynamic therapy of onychomycosis caused by Trichophyton rubrum. J Am Acad Dermatol. 2008;59:S75–6.
50. Sotiriou E, Koussidou-Ermonti T, Chaidemenos G, Apalla Z, Ioannides D. Photodynamic therapy for distal and lateral subungual toenail onychomycosis caused by *Trichophyton rubrum*: preliminary results of a single-centre open trial. Acta Derm Venereol. 2009;90:216–7.
51. Gilaberte Y, Aspiroz C, Martes MP, Alcalde V, Espinel-Ingroff A, Rezusta A. Treatment of refractory fingernail onychomycosis caused by non dermatophyte molds with methylaminolevulinate photodynamic therapy. J Am Acad Dermatol. 2011;65:669–71.
52. Sotiriou E, Panagiotidou D, Ioannides D. 5-Aminolevulininic acid photodynamic therapy treatment for tinea cruris caused by Trichophyton rubrum: report of 10 cases. JEADV. 2009;23:341–2.
53. Lee JW, Kim BJ, Kim MN. Photodynamic therapy: new treatment for recalcitrant *Malassezia* folliculitis. Laser Surg Med. 2010;42:192–6.
54. Pierard GE, Pierard-Franchimont C, Arrese JE. The boosted antifungal topical treatment (BATT) for onychomycosis. Med Mycol. 2000;38:391–2.
55. Goffin V, Arrese JE, Pierard GE. Onychomycoses récalcitrantes et le 'low-coast BOAT' au fluconazole. Skin. 2002;5:145–7.
56. Hao J, Smith KA, Li SK. Iontophoretically enhanced ciclopirox delivery into and across human nail plate. J Pharm Sci. 2009;98:3608–16.
57. Nair AB, Kim HD, Davis SP, Etheredge R, Barsness M, Friden PM, et al. An ex vivo toe model used to assess applicators for the iontophoretic ungual delivery of terbinafine. Pharmaceutical Res. 2009;26:2194–201.