



Review Article

The menace of hyperkeratotic tinea infection: A new therapeutic combination on horizon

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ABSTRACT

Background: Hyperkeratinization and changes in skin pH play very important role in pathogenesis of tinea infections resulting in treatment failure in multiple patients. The objective of the current consensus was to provide an experience-driven approach regarding the management of hyperkeratotic tinea infection with combination of topical antifungal and keratolytic agents.

Materials and Methods: 9 experts in the field of dermatology participated in digital meeting to discuss the role of combination of topical antifungal and keratolytic agent based on prevalidated questionnaire consisting of 18 questions. Questions were graded on a scale of 1 to 10 (1 being not recommended and 10 being strongly recommended).

Results: During the meeting panellists discussed regarding the pathophysiological aspects of hyperkeratotic tinea infection, impact of hyperkeratinization or scaling and changes in skin pH on management of patients with tinea infection, ideal topical antifungal and keratolytic agent and the rationale for combination, frequency, duration and method of application, initiation of therapy, safety of combination and precautions to be taken during treatment period. After the end of meeting total 18 recommendations were made based on a thorough discussion, available evidence and practical experience of the experts.

Conclusion: This consensus will help in management of patients with hyperkeratotic tinea infection and will improve the treatment outcomes in these patients.

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1. Background

The current scenario of tinea infections in India is very alarming and management of tinea infections has become a great therapeutic challenge for dermatologists. Patients

are presenting with unusually large, atypical, ring within ring, highly inflamed lesions. The current situation of tinea infections in India can be attributed to multiple factors, including more humid and warmer climate, irrational use of topical corticosteroid-based combinations, increased use of broad-spectrum antibiotics, increased burden of immune-compromised population, widespread use of antifungals

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in the agricultural industry, and the questionable role of antifungal drug resistance.¹⁻³

1.1. Issues

One of the challenging scenarios while managing patients with dermatophytosis is hyperkeratotic tinea infection. The complex interaction between host and fungus leading to hyperkeratinization or scaling and changes in skin pH also play very important role in pathogenesis of tinea infections.⁴⁻⁶ It has been seen that hyperkeratosis is associated with decrease in absorption and interfere with antifungal activities of topical antifungal agents especially topical azoles, similarly change in pH of the skin from acidic to alkaline medium in tinea infections is associated with increase in fungal virulence and host tissue damage.⁴⁻⁶ Common treatment options for hyperkeratotic dermatophytosis include topical antifungals, usually for up to 4 weeks. However, the efficacy of topical anti-mycotic as sole therapy often is limited in such conditions. The thick scale may impede absorption of the antifungal agent, is the common culprit. Consequently, adjunctive oral therapy for 1 to 4 weeks is often necessary, thereby contributing to the potential adverse effects and interactions of the drug.⁷

2. Scope and Objectives

In searching for better topical treatment of hyperkeratotic tinea infections, the characteristic thick scale must be addressed. It was therefore decided to set up an Expert Group meeting with the objective to bridge this need gap and provide an experience-driven approach regarding the management of hyperkeratotic tinea infection especially the role of keratolytic agents.

3. Materials and Methods

In order to gain insights on pathophysiological aspects and management of patients with hyperkeratotic tinea infection, a panel comprising of 9 expert dermatologists across India was selected according to their clinical experience, their interest in the field of infectious dermatology and use of keratolytic agents in management of tinea infection.

A questionnaire was predesigned after extensive literature search with respect to impact of hyperkeratinization, changes in skin pH, use of combination therapy, and role of keratolytic in the management of tinea infections. This questionnaire consisting of 18 questions was prevalidated with moderator of the panel and likely responses of these questions were converted into statements. A meeting was held on digital platform to enable discussion on these questions and at the end of meeting, the statements were put forth across the panelists, who voted for/against it on a scale of 1 to 10 (1 being not recommended and 10 being strongly recommended). Average for each statement score was taken from all the panelists' responses and

interpretation of these is as follows:

To 3: least/not recommended

4 to 7: neutral i.e. final decision to be taken by the dermatologist depending on clinical judgment on case to case basis.

To 10: Strong recommendation

4. Results

During the meeting panelists discussed regarding

1. The pathophysiological aspects of hyperkeratotic tinea infection
2. Impact of hyperkeratinization or scaling and changes in skin pH on management of patients with tinea infection
3. Ideal topical antifungal and keratolytic agent and the rationale for combination.
4. Frequency, duration and method of application, initiation of therapy.
5. Safety of combination and precautions to be taken during treatment period.

After the end of meeting total 18 recommendations were made based on a thorough discussion, available evidence and practical experience of the experts. The summary of key recommendations is as follows.

5. Discussion

As mentioned earlier, the clinical presentation of tinea infections has undergone a sea change which is attributed to plethora of factors. Hyperkeratinization and changes in skin pH have big impact on the management of patients with tinea infections. Combination of potent topical antifungal agent with potent keratolytic agent can be very useful in management of such patients. The main highlights of panel discussion related to these parameters and their possible impact on outcomes are furnished below.

5.1. Epidermal Hyperkeratinization and Tinea infections

Dermatophytoses are usually associated with several fold increase in epidermal cell proliferation leading to epidermal thickening with hyperkeratosis and scaling of the skin. Jensen JM et al in their study demonstrated that, there is 7-fold increase in keratinization in tinea corporis in the lesional skin compared to non lesional skin.⁶ LEE WJ et al in their study also reported the similar results.⁸

It has also been observed that the epidermal proliferation or hyperkeratinization in tinea infections is associated with increased in expression of pro-inflammatory keratins like K6, K16, and K17, disturbances in expression of basal keratins K5 and K14 and reduced expression of differentiation-associated K10.⁶ Koga et al in their study

Table 1:

Recommendation	Average score
The complex interaction between host and fungus leading to hyperkeratinization or scaling and changes in skin pH plays very important role in pathogenesis of tinea infections.	8.7
Dermatophytoses are usually associated with several fold increase in epidermal cell proliferation leading to epidermal thickening with hyperkeratosis and scaling of the skin.	9.0
Hyperkeratosis and scaling of skin in patients with tinea infection is associated with decrease in absorption and interference with antifungal activity of topical antifungal agents.	8.5
Dermatophytes are associated with change in skin pH which may contribute to host tissue damage and thereby enhancing the virulence of the dermatophytes.	8.4
Combination of potent topical antifungal agent along with potent keratolytic agent may be very useful in tackling the menacing scenario of hyperkeratotic tinea infection.	8.9
Luliconazole should be the first choice of topical antifungal agent because of its multimodal mechanism of action, broad spectrum of activity, low MIC values and high sensitivity against dermatophytes and low binding affinity for keratin.	9.3
Salicylic acid should be considered in the management of hyperkeratotic tinea infections because of its potent keratolytic activity and pH lowering activity.	8.8
The combination is indicated in the management of hyperkeratotic tinea infections like tinea pedis, tinea mannum, moccasin type of tinea pedis, tinea corporis, etc.	8.9
The combination should be "used cautiously" in patients with involvement of more than 10% body surface area or involvement of sensitive areas of the skin like groin, face, axilla, etc.	8.9
Ideal duration of therapy with combination should be 2-3 weeks.	9.1
The combination should be applied once daily preferably at night.	8.9
The rule of 2 is not applicable to the combination because of its irritation potential.	7.8
In patients with confirmed hyperkeratotic tinea infection therapy should be initiated with combination.	8.8
The combination therapy can also be initiated in those patients who are not responding to antifungal agents alone and patients with signs of hyperkeratosis.	7.1
No other topical antifungal should be used along with combination.	7.3
Barrier repair creams or moisturizers should be used as an adjuvant to reduce the irritation associated with combination.	9.2
In general, salicylic acid is well tolerated however the risk of salicylism should be taken into consideration while prescribing combination.	8.2
The combination should not be used in patients <12 years of age or geriatric age group because of increased chances of irritation owing to thin and sensitive skin. It should be avoided in pregnancy and lactation as safety data in these special population is lacking.	9.2

reported that trichophytin stimulated production of INF- γ and IL2 was markedly decreased in patients with hyperkeratotic tinea infections resulting in decreased clearance of fungi and thus treatment failure.⁹

Hyperkeratinization creates a favourable environment for dermatophytes to grow by providing more keratin as food for fungus. Excess keratin also interferes with the antifungal activity of antifungal agents. Antifungal drugs especially azoles have reported to possess high-binding affinity to keratin. Binding of the drug to keratin inactivates the drug and reduces the availability of the free drug.¹⁰ Hyperkeratinization is also associated with reduced penetration of antifungal drugs firstly because of physical barrier due to scaling and secondly, the bound form of the drug does not contribute to the concentration gradient due to the lack of thermodynamic activity. This decreases the amount of drug penetrating into the deeper layers.¹¹

After considering all these facts the experts agreed upon the fact that hyperkeratinization do play significant role in pathogenesis of tinea infections leading to increased inflammation, reduced clearance of dermatophytes,

chronicity of the disease and interference in activity of antifungal drugs.

5.2. Changes in skin pH and tinea infections

The average skin surface and nail plate pH is 4.7, with the skin presenting a pH gradient in which the upper layers are acidic and the pH increases in the deeper layers.^{4,5} The skin pH gradient is important for the proper regulation of the activity of enzymes involved in the keratinisation process that is essential for the removal of dead cells and renewal of the stratum corneum. Surface acidic pH is also an important defence against growth of microorganisms, mainly because a number of microbial infections are commonly associated with higher skin pH values. Moreover, acidification of the stratum corneum is required for the formation of a functionally competent permeability barrier that is involved in several key stratum corneum functions.^{4,5}

It has been observed that dermatophytes are associated with significant changes in skin pH from acidic to alkaline environment. This shift in the extracellular pH value from

acidic to alkaline, contributes to host tissue damage and thereby enhancing the virulence of the dermatophytes. Also, the change in ambient skin pH are associated with overexpression of genes encoding several proteases and membrane transporter proteins which lead to establishment and chronicity of dermatophytic infection.^{4,5} Further more Kim HJ et al in their study reported that the application of topical steroids is also associated with increase in skin pH and decrease in skin barrier function.¹²

Experts agreed upon these facts and commented that the changes in skin pH should be considered while managing patients with tinea infections and use of topical agents which normalizes the skin pH should be considered.

5.3. Combination of topical antifungal and keratolytic agent in Tinea infections

Considering the above-mentioned pathological factors, experts commented that the combination of potent topical antifungal agent along with potent keratolytic agent should be considered in management of tinea infections.

According to experts, following rationale justifies the use of combination therapy:

Kircik LH et al in their study commented that the treatment of tinea pedis with hyperkeratosis has always been challenging due to presence of thick scales even after the resolution of active fungal infection.¹³

Keratolytic reduces hyperkeratinization and scales by increasing desquamation process thus helps in reducing fungal load by increasing the shedding of stratum corneum where dermatophytes resides.^{1,7} Keratolytics can also be helpful in increasing the penetration of antifungal agent by removal of scales and superficial part of stratum corneum thus improving the antifungal activity.^{14,15}

Various clinical trials have shown the better efficacy with combination of antifungal agent plus keratolytic in tinea infections. Elewski BE et al in their study concluded that combination of topical antifungal, ciclopirox along with keratolytic agent urea gave optimal outcomes in management of hyperkeratotic tinea pedis.⁷ Moreover, patients usually identify hyperkeratosis with active disease. Therefore, a regimen of an antifungal and a keratolytic agent would be useful not only clearing the skin clinically but also addressing patients' perceptions.¹³

5.4. Choice of Topical antifungal and keratolytic agent

Out of multiple available topical antifungal agents, luliconazole was considered as a drug of choice to be used in combination of keratolytic agent due to its multimodal mechanism of action, lower minimum inhibitory concentration (MIC) values and very high sensitivity against various dermatophytic species like *T. mentagrophytes*, *T. verrucosum* and *T. rubrum* compared to other topical antifungal agents.¹⁶⁻¹⁹

Regarding the choice of keratolytic agent, 3% salicylic acid was considered because of its role in the management of tinea infection, its potent multimodal keratolytic activity with added advantage of acidic pH.^{20,21}

5.5. Luliconazole (1%): Role in Tinea infections

Luliconazole is an imidazole antifungal agent with potent and broad antimycotic activity. Primary mechanism of action of luliconazole is inhibition of ergosterol biosynthesis by inhibiting the enzyme 14 α demethylase thus reducing the conversion of lanosterol to ergosterol. It has also been demonstrated that luliconazole significantly reduced the amount of adenosine triphosphate in fungus resulting in reduced energy production. Apart from this, luliconazole has also been exhibited to inhibit extracellular protease secretion in fungus, which is known to play an important role in pathogenesis of tinea infections. Because of these multi modal mechanisms of action luliconazole has very broad spectrum of activity against all the pathologically relevant fungi like dermatophytes, candida spp. and molds.¹⁶ Another important fact regarding luliconazole is its very low MIC values compared to other antifungal agents making luliconazole most potent antifungal agent available.¹⁷ Recently published study by Das et al concludes that luliconazole is the most potent topical antifungal agent with sensitivity in the range of 80 – 90% against *T. verrucosum*, *T. Mentagrophytes* and *T. Rubrum* compared to other topical antifungal agents with sensitivity in the range of 20 – 60%.¹⁸

Compared to other azoles, luliconazole possess very low binding affinity for keratin which allows luliconazole to be released from the keratinous tissues easily. Thus in contrast with many other azoles, its potency remains unaffected by keratin.^{16,19}

Because of its multimodal mechanism of action, high potency, no issue of resistance and extensive clinical experience with luliconazole, experts recommended that luliconazole should be considered as first choice topical antifungal in management of tinea infections.

5.6. Salicylic Acid (3%): Potent Keratolytic Agent

Salicylic acid has been used to treat various skin disorders since ages. The ability of salicylic acid 3 – 6% to exfoliate the stratum corneum makes it a gold standard keratolytic agent. Salicylic acid acts via multiple pathways to increase the desquamation of keratinocytes these includes^{14,20}

- Being a lipophilic agent, SA removes intercellular lipids, which are linked covalently to the cornified envelope surrounding the surface epithelial cells. Thus, SA decreases adhesion of corneocytes, and causes loosening of these cells and their subsequent detachment.^{14,20}
- Cohesion of epidermal cells in the skin depends upon desmosomes, which contain many proteins, including

desmogleins. It has been found that SA, being an organic acid, extracts desmosomal proteins including desmogleins. As a result of this action, the cohesion of epidermal cells is lost, leading to exfoliation.^{14,20}

- Salicylic acid is also associated with lowering of pH of the skin resulting in increased hydration of the keratin and swelling of the corneocytes.^{14,20}

This multimodal action of SA can be very beneficial in management of tinea infection because Increase in desquamation and keratolysis leads to reduction in fungal load by removing the excess keratinocytes where fungi lives. Salicylic acid helps in facilitation of penetration/absorption of topical agents when used in combination, which is proven in studies.^{14,15}

Being an acid, it reduces the pH of the stratum corneum, thus salicylic acid may help in regulating the activity of enzymes involved keratinization and improving natural defensive barrier of the skin against microorganisms. Thus, it also helps to address one of the key pathogenic factor in tinea infections i.e. change in pH of skin from acidic to alkaline range, which might play an important role in improving outcome.

Various guidelines, textbooks and few studies recommend the use of salicylic acid 3 – 6% in management of tinea infections. 3% salicylic acid has been in use in the form of Whitfield's ointment for the treatment of superficial fungal infection since long.²¹ IADVL (Indian Association of Dermatologists, Veneriologists and Leprologists) manual of tinea infections mentions 3 – 6% salicylic acid as an adjuvant in the treatment of tinea infections, to increase the penetration of topical antifungals.²² Expert consensus on management of tinea infections in India i.e. ECTODERM India guidelines also recommend the combination of topical antifungal with 3 – 6% salicylic acid.¹ Goldstein AO et in their review recommend the use of 3% salicylic acid in management of tinea infections.²³ Saoji et al in their study concluded that “Salicylic acid peel is a cheap and useful option in the treatment of dermatophytic infection”.²⁴ Recently published consensus by IADVL task force against recalcitrant tinea (ITART) on the management of glabrous tinea also recommends the use of keratolytic like salicylic acid in hyperkeratotic tinea infection.²⁵

Experts recognized these facts regarding salicylic acid and thus recommended that salicylic acid can play significant role in management of hyperkeratotic tinea infections.

5.7. Placement of combination in the management of tinea infections

5.7.1. Clinical profile of patients where combination is recommended

According to experts, the combination of luliconazole and salicylic acid should be recommended in patients with hyperkeratotic tinea infections. Experts also commented

that the combination can also be used in patients with recalcitrant tinea infections associated with thick scaling and not responding to antifungal agents alone.

5.7.2. Frequency, duration and method of application

The experts recommended that the ideal duration of therapy with combination of luliconazole with salicylic acid should be 2 weeks. The therapy can be extended by another 1 week if the hyperkeratosis is severe. The ideal frequency of application according to experts would be once daily depending upon the severity of disease.

In current scenario of tinea infections in India, “The rule of Two” is practised by majority of dermatologists. According to this rule, the topical antifungals should be applied 2 cm beyond the margin of the lesion for at least 2 weeks beyond clinical resolution.²⁶ However according to experts this rule is not applicable to the combination because of irritation potential of salicylic acid.

5.7.3. Initiation of therapy

Experts recommend that in cases with confirmed hyperkeratotic tinea infection therapy should be initiated with combination of luliconazole and salicylic acid for first 7 to 14 days. Experts also commented that the combination therapy can also be initiated in those patients who are not responding to only antifungal agents and patients with signs of hyperkeratosis.

5.7.4. Safety profile of combination

In various clinical trials luliconazole was associated with application site reactions like itching, irritation, pain and redness.^{27,28} However, all these reactions were of mild severity and were not associated with discontinuation of therapy. Similarly, topical salicylic acid is also associated with mild application site reactions like dryness, irritation and contact sensitization. In clinical trials salicylic acid when used in various concentration in the range of 3 – 30% was not associated with any significant serum level of salicylic acid and has not resulted in any major side effects.^{29,30}

Since, both topical luliconazole and salicylic acid are generally well tolerated, experts were of the opinion that the combination of luliconazole and salicylic acid can be associated with tolerable safety profile. Experts also highlighted the theoretical risk of salicylism associated with use of topical salicylic acid and recommended that precautions should be taken while using combination in patients with tinea infections involving large body surface area, patients with co-morbidities and alcoholism. Patients should be counseled regarding adverse effects and risk of salicylism.

5.7.5. Precautions and use in special population

As discussed earlier since both salicylic acid and luliconazole may be associated with skin irritation and application site reactions, experts recommended that use of combination should be avoided in areas with sensitive skin like genital area, intertriginous areas, face, etc. The duration of therapy should be strictly restricted to 2 weeks only.

According to experts, the use of combination should be restricted only to management of patients with hyperkeratotic tinea infection and should not be used in all the patients with tinea infections. It was also agreed that the patients should be counseled regarding the adverse event associated with combination to improve patient compliance. In patients with moderate to severe adverse reactions experts advised use of barrier repair creams or moisturizers as an adjuvant to reduce the irritation associated with combination.

Even though both luliconazole and salicylic acid are safe in pediatric and geriatric age group, experts were of the opinion that the use of combination should not be used in patients <12 years of age or geriatric age group because of increased chances of irritation owing to thin and sensitive skin. The combination is not recommended in pregnant females or during lactation because of lack of safety data.

6. Conclusion

Hyperkeratinization and changes in skin pH plays very important role in pathophysiology of tinea infection and have big impact on management of patients with hyperkeratotic tinea infection. Combination of potent topical antifungal and keratolytic agent should be considered as first choice therapy in such patients. Luliconazole is potent and broad-spectrum antifungal agent while salicylic acid is gold standard keratolytic agent. Thus, the combination of both the drugs may have synergistic activity. Salicylic acid will help in removal of excess keratinocytes resulting the increased penetration of drugs and reduction in fungal load. It will also reduce the skin pH and keratin concentration thus reducing its interference on antifungal activity of luliconazole. Luliconazole being a potent antifungal drug will help in eradication of fungus. The combination therapy may be associated with faster clearance of lesions because of their synergistic activity and may reduce the duration of antifungal therapy.

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9. Conflict of Interest

The authors declare they have no conflict of interest.

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