REVIEW ARTICLE

Non-pharmacological treatment modalities for onychomycosis A systematic review

[1]Manish Rijhwani, MD, [2]Priyanka Sharma, [2]Divya Yadav, [3]Manisha Nijhawan, MD

[1]Associate Professor, [2]Resident, [3]Professor & Head
Department of Dermatology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India

ABSTRACT

Background: Onychomycosis is a fungal infection of the nails caused by dermatophytes, non-dermatophytes and yeasts. The condition affects around 10–30% people worldwide and has a negative influence on patient's quality of life. The nail unit acts as a barrier to exogenous substances, its physiological features interfere with drug penetration, which makes treatment of onychomycosis a challenge. The aim of this article is to discuss non-pharmacological approach for management of onychomycosis.

Methods: Electronic database from PubMed was searched systematically to identify relevant articles published from 2001-2021. Potentially relevant articles were sourced, assessed against eligibility criteria and data were extracted from included studies. A meta-analysis was performed to identify non-pharmacological treatment modalities for onychomycosis.

Results: The systematic search of the literature identified 509 potentially relevant articles. Eighteen articles which met the eligibility criteria involving 727 patients were evaluated. The specific and relevant data from each of these articles was extracted. The results of this analysis revealed that the overall mycological cure rate in onychomycosis with laser treatment was 48.0%. Overall efficacy of photodynamic therapy showed mycological cure rate of 56.3%. Efficacy of 40% urea in comparison with 5% amorolfine lacquer was found to be 32%. Combination of surgical avulsion and topical therapy for onychomycosis showed 56% mycological cure rate.

Conclusion: Laser treatment for the treatment of onychomycosis has a high mycological cure rate and high safety profile. Nail avulsion in combination with topical antifungal therapy was found to be moderately efficient. Methylene blue photo dynamic therapy demonstrated promising and safe results for non-dermatophyte onychomycosis. 40% Urea as an adjunct to standard treatment regimens showed promising results in treatment of onychomycosis.

KEY WORDS: Onychomycosis, Laser, Photodynamic therapy, Nail avulsion

INTRODUCTION

Onychomycosis is a chronic fungal infection of the nail causing hyperkeratosis and eventual onycholysis and thickening of the nail plate due to dermatophytes and non-dermatophytes. In more than 90% of patients, onychomycosis is caused by a dermatophyte infection from the genera Trichophyton (most commonly *T. rubrum* and *T. mentagrophytes*), Epidermophyton or Microsporum.[1] In rare cases, non-dermatophyte molds (e.g. *Aspergillus niger* or *Scytalidium dimidiatum*) and yeasts (e.g. *Candida albicans*) can also cause onychomycosis.[2]

Five categories of onychomycosis have been established: distal and lateral subungual, superficial white, proximal subungual, endonyx and total dystrophic onychomycosis. The most common form of the disease is distal and lateral

Correspondence: *Dr Divya Yadav, Department of Dermatology, Mahatma Gandhi Medical College and Hospital, Jaipur, Rajasthan, India*

subungual onychomycosis.[3] It is characterized by fungal infection of the nail bed, causing hyperkeratosis and eventual onycholysis and thickening of the nail plate.[4] Risk factors for onychomycosis include age, diabetes, peripheral vascular disorders and immunosuppression. Chalky white patches appear on the nail, leaving the surface crumbly and soft. Proximal subungual onychomycosis is the most common form of onychomycosis among patients infected with human immunodeficiency virus (HIV) and those with immunocompromised conditions. Rare instances of dermatophytes spreading proximally or distally via the lymphatic system or bloodstream have been reported.[5]

Non-pharmacological treatment modalities for onychomycosis includes photodynamic therapy (PDT), laser therapy, chemical and surgical nail avulsion. Photodynamic therapy uses visible spectrum light to activate a topically applied photosensitizing agent, which generates reactive oxygen species that initiate apoptosis. Photodynamic therapy was originally optimized for actinic keratosis, but photosensitizers can also be absorbed by fungi. Existing literature shows that photodynamic therapy is well tolerated and safe, it promotes a favourable outcome with good patient adherence and may be considered as a practical and feasible treatment option for onychomycosis.[6]

Laser therapy for onychomycosis is amongst the most popular therapeutic option today. The capacity to concentrate energy with determinate wavelength in such a small area, makes it the ideal treatment option. It acts by generating a structural and functional deterioration of the fungal cells and provokes the end of the infectious activity of the fungus. Apfelberg[7] studied laser treatment for onychomycosis in 1989, and since that time laser treatments such as long-pulsed 1064-nm. Nd: YAG lasers, short-pulsed 1064-nm Nd: YAG lasers, CO2 lasers and lasers with wavelengths of 870nm, 930nm and 1320nm have begun to emerge as new therapies for treatment of onychomycosis.[8]

The surgical removal of the nail in combination with systemic antifungals is amongst the emerging therapies for onychomycosis. However, it must be assessed with caution due to post-operative complications, poor aesthetical and functional result, and risk of anomalous growth of the nail with the consequent risk of recurrence. Chemical nail avulsion with topical urea cream has been suggested to improve the efficacy of topical antifungal treatments by improving penetration and bioavailability of topical agents. Urea, in concentrations over approximately 30%, is considered a keratolytic agent that softens and hydrates the nail plate by denaturing the nail keratin and thus enhancing the drug penetration and promoting the avulsion of affected nails.

METHODS AND MATERIALS

Search strategy and eligibility criteria

All data of this study were collected from published trials, so an additional ethical approval is not necessary. The study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched electronic databases (PubMed) for studies published from 2000-2021 using the Mesh terms “laser, onychomycosis”, “surgery, onychomycosis”, “photodynamic therapy, onychomycosis" and “chemical removal, onychomycosis”.

Inclusion criteria:

1. Randomized Controlled Trial (RCT) or clinical study in which the onychomycosis group received laser treatment.
2. Onychomycosis diagnosed by mycological examination.
3. Studies including surgical treatment in combination with topical antifungals for onychomycosis.
4. Studies on photodynamic therapy in combination with topical antifungals as treatment modality.
5. Studies including chemical avulsion as a treatment modality for onychomycosis.
6. Patients had not been treated with systematic antifungal drugs during the preceding 6 months.

Exclusion criteria:

1. Studies with monotherapy of topical, and systemic antifungals used as treatment modality for onychomycosis were excluded.
2. Case reports and case series on onychomycosis
3. Duplicate records.

Study selection:

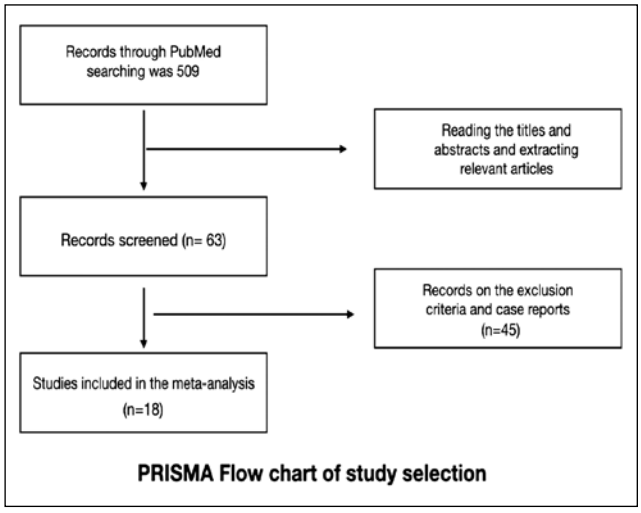
Articles were initially assessed by title and abstract only. Those not meeting the inclusion criteria were excluded. Full text of the remaining articles was retrieved and assessed to determine eligibility for inclusion in the study. Study selection and data extraction was done and the final results was cross-checked.

Data extraction:

Relevant information was extracted from publications meeting the inclusion/exclusion criteria.

Statistical analysis:

A meta-analysis of the efficacy of laser treatment, photodynamic therapy, chemical and surgical nail avulsion for onychomycosis was performed using extracted data from included studies.



PRISMA Flow chart of study selection

LIST OF STUDIES INCLUDED

Author	Study design	Treatment method	Number of patients	Number of diseased nails	Cure rate
J.F.J Rovers[9] (2020)	Retrospective	1064 nm N:D YAG laser pulse at three occasions, with a treatment interval of 2 weeks. Duration: 20–30 ms, fluence: 60 J/cm^2, cooling DCD 40/20	113	714	55.5 %
Wanitphakdeedecha R[10] (2015)	RCT	1064-nm Nd:YAG laser in four sessions at 1-week intervals. 4-mm spot size with fluence of 35 to 45 J/ cm^2, pulse duration of 30 to 35 ms and frequency of 1 Hz	35	64	51.9 %

Ortiz AE[11] (2014)	RCT	1320-nm Nd: YAG laser; pulse width:350 ms; spot size: 5 mm; frequency: 20 HZ in four sessions (on day 1, 7, 14 and 60)	10	20	50 %
Landsman[12] (2016)	RCT	870-nm+930-nm laser; energy: 424 J/cm^2; spot size: 1.5 cm in four sessions (on day 1, 14, 42 and 120)	34	53	38 %
Hollmig (2014)[13]	RCT	1064-nm ND: YAG laser (fluence of 5 J/cm^2, rate of 6 Hz) spaced 2 weeks apart	25	125	33 %
Zhou (2016)[14]	RCT	Laser: CO_2 fractional laser; energy: 10 mJ; spot size: 4 – 10 mm with Drug: 1% luliconazole. Laser treatment: once every two weeks for six months	60	223	53 %
Bhatta A. K[15] (2016)	RCT	Fractional CO_2 laser using pulse energy of 99 mJ, a density of 410 spots/cm^2, pulse interval of 0.5 mm, pulse duration of 0.1 milliseconds, and a rectangular spot size of 2- to 10-mm length and 0.6- to 5-mm breadth and once-daily application of terbinafine cream for 3 months.	75	356	78.18 %
Moon[16] (2014)	Self- control	The long-pulsed 1064-nm Nd-YAG laser; energy: 5 J/cm^2; pulse width: 0.3 ms; spot size: 6 mm; frequency: 5 Hz: Five sittings at four-week intervals	13	43	70 %
Karsai[17] (2016)	RCT	The short-pulsed 1064-nm Nd-YAG laser; energy: 20 J/cm^2; pulse width: 0.1 ms; spot size: 1.5 mm; frequency: 30 Hz: Four sessions with an interval of 4-6 weeks	20	82	0 %
Kimura[18] (2012)	Self -control	The short-pulsed 1064-nm Nd-YAG laser; energy: 14 J/cm^2; pulse width: 0.3 ms; spot size: 5 mm; frequency: 5 HZ: Three treatment episodes for 7 people, two for 5 people and one for 1 per- son, with a treatment interval of 4 weeks	13	37	51%
Joao Paulo Tardivo[19] (2015)	Small-scale trial	A 1:1 volume of the 2% methylene blue/2% toluidine blue mixture applied between the nail plate and nail bed. After 5 min the nail was irradiated superficially with the RL50 source at a distance of 5 cm for 3 min, providing a final irradiance of 18 J/cm^2	62	----------	45 %
Souza LW[20] (2014)	Open- label controlled clinical trial	2% aqueous MB solution applied followed by irradiation with red light (630 nm, 36 J/cm^2) from an LED device with a light intensity output of 3100 mW/cm^2 and optical intensity of 100 mW/cm^2	22	----------	63.6 %

Eleni Sotiriou[21] (2009)	Single-centre Open Trial	20% 5-ALA applied under an occlusive dressing topically after nail plate and subungual hyperkeratosis removal – treated 3 h later with red light (570–670 nm) from a non-coherent light source at a light dose of 40 J/cm^2: fluence rate of 40 mW/cm^2: 3 times at 2-weekly interval	30	30	43.3 %
N. Bowornsathitchai[23] (2021)	RCT	Methylene blue-mediated photodynamic therapy (MB-PDT) given every two weeks for a total of six sessions	10	15	73.3 %
Bunyaratavej S[22] (2016)	Case- control	40% urea 5% amorolfine lacquer	26 27	---------	32 % 89.3%
Bassiri -Jahromi[24] (2012)	RCT	40% urea with 1% fluconazole cream (in combination) once daily for 6 months	70	----------	82.8%
Lahfa[25] (2013)	RCT	40% urea then 1% bifonazole cream (urea as adjunct) 40% urea with 1% bifonazole cream (urea in combination)	51 51	----------	42.6 % 58.3%
C. Grover[26] (2007)	RCT	Combination of surgical avulsion and topical antifungal therapy for single nail onychomycosis .	40	40	56 %

RESULTS

The systematic search of the literature identified 509 potentially relevant articles. After removing duplicate publications 63 articles remained and were subjected to preliminary screening. Following the exclusion of descriptive studies, studies that included monotherapy with topical and systemic antifungals, case series and case reports, 18 articles remained that met the eligibility criteria. These 18 articles involved 727 patients. The specific and relevant data from each of these articles was extracted.

The results of this analysis revealed that the overall mycological cure rate in onychomycosis of laser treatment was 48.0%. The mycological cure rate of long pulse width 1064-nm Nd:YAG laser treatment was 49.7%, the mycological cure rate of short pulse width 1064-nm Nd:YAG laser treatment was 25.5%, the mycological cure rate of CO_2 fractional laser treatment was 65.5%.

According to the literature, ND: YAG laser therapy was found safe. Patients treated with a ND:YAG laser at three occasions, with a treatment interval of 2 weeks followed by potassium hydroxide examination and fungal culture showed significant improvement. Subgroup analyses revealed better results in women. There were no serious complications reported after this treatment modality. A study reported subsequent hemorrhage occurred after treatment with CO_2 laser and subsided after 2 weeks. After reducing the laser energy density, there was no evidence of bleeding.[27] Though pain was frequently reported during the treatment, it subsided immediately after the therapy and was a limiting factor to increase the laser power.

The overall efficacy of photodynamic therapy in onychomycosis was found to be 56.3%.

Mycological cure rate at 22 weeks, in Methylene Blue-Photodynamic therapy (73.3%) was

slightly higher than amorolfine (66.67%) and clinical cure rate at 22 weeks, in Methylene Blue-Photodynamic therapy (26.7%) was higher than amorolfine (16.7%) although this was not statistically significant

The most frequently reported side effects following photodynamic therapy were: pain/ burning/stinging sensation (45.5%), erythema (37.3%), blistering (9.3%), oedema (28.2%%), hyper/hypo-pigmentation (7.1%%).

Among MAL-PDT patients that reached mycological cure, 67% reached complete cure, 17% reached treatment success and 17% reached clinical improvement. Efficacy of 20% 5-ALA applied under an occlusive dressing topically after nail plate and subungual hyperkeratosis removal was reported to be 43.3%. Efficacy of 40% urea in comparison with 5% amorolfine lacquer was found to be 32%. Combination of 40% urea with 1% fluconazole showed 82.8% efficacy and combination of 40% urea with 1% bifoconazole showed 42.6%. Side effects were negligible and recurrence rate was 4.2% in patients.

Combination of surgical avulsion and topical therapy for onychomycosis showed 56% mycological cure rate. Occlusion improved the treatment outcome of nail avulsion. 71% of the total patients receiving occlusion achieved a mycological cure vs 38% receiving no occlusion.

DISCUSSION

Onychomycosis is a mycotic disease of the nail unit caused by dermatophytes, yeasts, and molds. Dermatophyte infection of the nail unit is the most common cause of onychomycosis.

1064 nm long pulsed laser inhibits growth of the fungus while CO_2 laser increases the localized temperature and decompose the infected tissue and have sterilizing effect. The cytoderm of Trichophyton fungi contains a large amount of melanin, and the absorption spectrum of its chromophore is 1064nm hence, long-pulsed 1064-nm Nd:YAG laser can act directly on the chromophore, resulting in a localized increase in temperature and subsequent destruction of the fungi. The short-pulsed 1064-nm Nd:YAG laser acts on the diseased nail, resulting in tiny bubbles to form and producing sonic shock waves which significantly inhibit the growth of the fungal colony.

The overall efficacy of laser treatment was moderately lower than that of conventional oral drug treatments, but it produced less reported side effects, such as damage to the liver and kidney or gastrointestinal reactions.

In a study done by Karsai et al[17] it was reported that short-pulsed 1064-nm Nd:YAG laser treatment had no effect on either the mycological cure rate or on clinical improvement of onychomycosis caused by *T. rubrum*. J.F.J Rovers et al[9] postulated that the only factor that might increase efficacy of ND: YAG laser therapy for onychomycosis could be increasing the power (Joules, pulse duration and number of passes). A major drawback here is pain perception during treatment. The literature included in our study and other similar studies have shown laser-assisted topical therapy could be as effective as combination therapy.

Photodynamic therapy is a photochemical process, which involves the combination of non-toxic photosensitizers and the exposure of light. The main mechanism of photodynamic therapy for treatment of onychomycosis is generation of

reactive oxygen species providing broad spectrum antimicrobial effect including fungicidal properties.[28] Studies have shown that PDT can successfully treat onychomycosis in patients where conventional therapy failed or patient could not continue therapy due to adverse effect. The main problem in using PDT for onychomycosis is inadequate penetration of photosensitizing drug via nail plate. To overcome this hurdle, most of the studies used urea as a pre-treatment to soften the nail or micro-abrasion of the nail and/or complete removal of nail plate was employed.

Chemical avulsion aims to dissolve the bond between the nail plate and the nail bed, and this softens the nail plate.[29] Different urea ointments (e.g - 40% urea, 20% urea with 10% salicylic acid, 40% urea with the topical antifungal bifonazole 1%) placed under occlusion for 1 to 2 weeks have been traditionally used to achieve chemical avulsion, and the diseased part of the nail is then removed with the use of a nail elevator and a nail clipper. Chemical avulsion is associated with minimal to no pain and has a low risk of infection and hemorrhage. When it is used as an adjunct treatment for topical antifungals, it increases the accessibility of the fungal mass. Disadvantages of this procedure include prolonged treatment duration, particularly when the procedure needs to be repeated. Urea treatment is generally associated with an unpleasant odour. Few cases of irritation following chemical treatment have been reported. Chemical avulsion may be recommended for the treatment of single nail onychomycosis during an early stage of the disease.[30] Chemical avulsion followed by topical terbinafine has been successfully used to treat onychomycosis caused by non-dermatophyte molds.

Surgical removal of the nail plate is another treatment option in the armamentarium, which always needs to be supplemented by some form of antifungal therapy. An efficacious topical treatment alternative for onychomycosis involves applying antifungal agents in combination with removal or debridement of infected nail unit.[31] It can be advised in patients who do not wish to opt for prolonged oral therapy and are at risk of adverse effects. However, it cannot be recommended in less severe forms of onychomycosis and was proven to be less effective.

CONCLUSION

This review identifies a limited number of studies, of varying methodological quality, that examine the efficacy and safety of various non-pharmacological treatment modalities for onychomycosis. Laser treatment of onychomycosis has shown high mycological cure rate and high safety record and can be used successfully for the treatment and cure of onychomycosis.

The present study suggests that PDT mediated by MB, MAL or ALA is a safe and effective method with satisfactory results in the treatment of mild-to-moderate toenail onychomycosis. Urea as an adjunct to standard treatment regimens, may improve the efficacy of treatment. Urea alone, however, does not appear to be superior to standard treatments. Treatment of single nail onychomycosis with avulsion in combination with topical antifungal therapy can be recommended selectively for use in patients who do not want prolonged oral therapy or are at risk of side-effects. However, further research and evaluation in larger patient population would be required to determine safety and efficacy of non- pharmaco-

logical modalities.

REFERENCES

1. Scher RK, Rich P, Pariser D, Elewski Bl. The epidemiology, aetiology, and pathophysiology of onychomycosis. Semin Cutan Med Surg. 2013; 32(2 Suppl 1):S2-4.
2. Elewski BE. Onychomycosis: pathogenesis, diagnosis, and management. Clin Microbiol Rev. 1998; 11:415-29.
3. Faergemann J, Baran R. Epidemiology, clinical presentation and diagnosis of onychomycosis. Br J Dermatol 2003; 149 Suppl 65:1-4.
4. Ellis DH. Diagnosis of onychomycosis made simple. J Am Acad Dermatol 1999; 40(6 Pt 2):S3-8.
5. Hay RJ, Baran R. Deep dermatophytosis: rare infection sorcommon, but unrecognized, complications of lymphatic spread? Curr Opin Infect Dis 2004; 17(2):77-79.
6. Figueiredo souza LW, Souza SV, Botelho AC. Randomized controlled trial comparing photodynamic therapy based on methylene blue dye and fluconazole for toenail onychomycosis. Dermatol Ther. 2014:27 (1): 43-47.
7. Apfelberg DB, Rothermel E, Widtfeldt A, et al. Preliminary report on use of carbon dioxide laser in podiatry. J Am Podiatry Assoc 1984; 74:509-13.
8. Ledon JA, Savas J, Franca K, et al. Laser and light therapy for onychomycosis: a systematic review. Laser Med Sci 2014; 29:823-29.
9. Rovers JFJ, Wagter LV, Greijmans EGE, Bovenschen HJ. 1064-nm Nd:YAG laser treatment for onychomycosis: is it worthwhile? Lasers Med Sci. 2021 Mar;36(2):463-467.
10. Wanitphakdeedecha R, Thanomkitti K, Bunyaratavej S, Manuskiatti W. Efficacy and safety of 1064-nm Nd:YAG laser in treatment of onychomycosis. J Dermatolog Treat. 2016;27(1):75-9.
11. Ortiz AE, Truong S, Serowka K, Kelly KM. A 1,320-nm Nd: YAG laser for improving the appearance of onychomycosis. Dermatol Surg. 2014 Dec;40(12):1356-60.
12. Landsman AS, Robbins AH. Treatment of mild, moderate, and severe onychomycosis using 870- and 930-nm light exposure: some follow-up observations at 270 days. J Am Podiatr Med Assoc. 2012 Mar-Apr;102(2):169-71.
13. Hollmig ST, Rahman Z, Henderson MT, Rotatori RM, Gladstone H, Tang JY. Lack of efficacy with 1064-nm neodymium: yttrium- aluminum -garnet laser for the treatment of onychomycosis: a randomized, controlled trial. J Am Acad Dermatol. 2014 May;70(5):911-7.
14. Zhou BR, Lu Y, Permatasari F, Huang H, Li J, Liu J, Zhang JA, Luo D, Xu Y. The efficacy of fractional carbon dioxide (CO2) laser combined with luliconazole 1% cream for the treatment of onychomycosis: A randomized, controlled trial. Medicine (Baltimore). 2016 Nov;95(44):e5141.
15. Bhatta AK, Keyal U, Huang X, Zhao JJ. Fractional carbon-dioxide (CO2) laser-assisted topical therapy for the treatment of onychomycosis. J Am Acad Dermatol. 2016 May;74(5):916-23.
16. Moon SH, Hur H, Oh YJ, Choi KH, Kim JE, Ko JY, Ro YS. Treatment of onychomycosis with a 1,064-nm long-pulsed Nd:YAG laser. J Cosmet Laser Ther. 2014;16(4):165-70.
17. Karsai S, Jäger M, Oesterhelt A, Weiss C, Schneider SW, Jünger M, Raulin C. Treating onychomycosis with the short-pulsed 1064-nm-Nd:YAG laser: results of a prospective randomized controlled trial. J Eur Acad Dermatol Venereol. 2017;31(1):175-180.
18. Kimura U, Takeuchi K, Kinoshita A, et al. Treating onychomycoses of the toenail: clinical efficacy of the sub-millisecond 1,064nm Nd: YAG laser using a 5 mm spot diameter. J Drugs Dermatol 2012; 11:496-504.
19. Tardivo JP, Wainwright M, Baptista M. Small scale trial of photodynamic treatment of onychomycosis in São Paulo. J Photochem Photobiol B. 2015;150:66-8.
20. Souza LW, Souza SV, Botelho AC. Distal and lateral toenail onychomycosis caused by Trichophyton rubrum: treatment with photodynamic therapy based on methylene blue dye. An Bras Dermatol. 2014;89(1):184-186.
21. E. Sotiriou, T. Koussidou-Eremonti, G. Chaidemenos, Z. Apalla, D. Ioannides, Photodynamic therapy for distal and lateral subungual toenail onychomycosis caused by Trichophyton rubrum: preliminary results of a single-centre open trial, Acta Derm. Venereol. 90 (2) (2010) 216-17.
22. Bunyaratavej S, Leeyaphan C, Rujitharanawong C, Surawan TM, Muanprasat C, Matthapan L. Efficacy of 5% amorolfine nail lacquer in Neoscytalidium dimidiatum onychomycosis. J Dermatol Treat. 2016; 27(4):359-63.
23. Bowornsathitchai N, Thammahong A, Shoosanglertwijit J, Kitsongsermthon J, Wititsuwannakul J, Asawanonda P, Boontaveeyuwat E. Methylene blue-

mediated photodynamic therapy may be superior to 5% amorolfine nail lacquer for non-dermatophyte onychomycosis. Photodermatol Photoimmunol Photomed. 2021;37(3):183-191.

24. Bassiri-Jahromi S, Ehsani AH, Mirshams-Shahshahani M, Jamshidi B. A comparative evaluation of combination therapy of fluconazole 1% and urea 40% compared with fluconazole 1% alone in a nail lacquer for treatment of onychomycosis: therapeutic trial. J Dermatol Treat. 2012;23(6):453-56.
25. Lahfa M, Bulai-Livideanu C, Baran R, Ortonne JP, Richert B, Tosti A, et al. Efficacy, safety and tolerability of an optimized avulsion technique with onyster (40% urea ointment with plastic dressing) ointment compared to bifonazole-urea ointment for removal of the clinically infected nail in toenail onychomycosis: a randomized evaluator-blinded controlled study. Dermatol. 2013; 226(1):5-12.
26. Grover, C., Bansal, S., Nanda, S., Reddy, B. and Kumar, V. Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. Brit J Dermatol. 2007;57:364-68.
27. Yang Y, Liu H, Yang RY, et al. The observation of efficacy of Ultrapulse CO2 fractional laser treatment for onychomycosis. Chin J Dermatol 2015;526-30.
28. Alberdi E, Gómez C. Methylene blue vs methyl aminolevulinate photodynamic therapy in the treatment of mild-to-moderate toenail onychomycosis: Short- and medium-term effects. Dermatol Ther. 2020;33(6):e14280.
29. Pandhi D, Verma P. Nail avulsion: indications and methods (surgical nail avulsion). Ind J Dermatol Venereol Leprol. 2012; 78:299-308.
30. Rollman O. Treatment of onychomycosis by partial nail avulsion and topical miconazole. Dermatologica. 1982; 165:54-61.
31. Cohen PR, Scher RK. Topical and surgical therapy of onychomycosis. J Am Acad Dermatol 1994; 31:574-77.