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Onychomycosis: A review of current pharmacological and non-pharmacological treatment options

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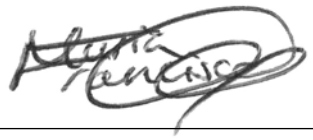

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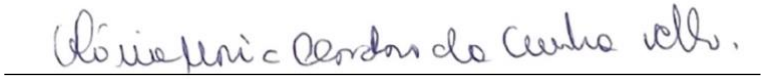

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RESUMO

INTRODUÇÃO: A onicomicose é uma infeção fúngica do leito ou da lâmina ungueal, com uma prevalência de cerca 10% na população geral, e representa um desafio terapêutico. Necessita de regimes terapêuticos prolongados, com taxas de cura pouco favoráveis, e elevada probabilidade de reinfeção. Atualmente, as opções incluem regimes longos de antifúngicos sistémicos e aplicação de vernizes tópicos durante vários meses. A opção sistémica está associada a várias interações farmacológicas e efeitos adversos, tornando-a pouco segura, sobretudo em doentes idosos e polimedicados, que constitui o grupo mais prevalente. Por outro lado, os regimes de aplicação tópica requerem que haja um cumprimento rigoroso dos mesmos, e apenas estão indicados para casos ligeiros a moderados, aos quais, ainda assim, oferecem taxas de cura limitadas. Tendo em conta esta realidade, torna-se necessária a análise das novas modalidades terapêuticas e os seus benefícios relativamente às taxas de sucesso e à qualidade vida dos doentes.

OBJECTIVOS: Esta revisão da literatura tem como intuito resumir, quer as opções de tratamento atualmente disponíveis, como as novas modalidades que demonstram resultados promissores e que merecem pesquisa adicional. É relatada uma abordagem completa das onicomicoses, desde o diagnóstico ao tratamento, incluindo ainda uma análise dos fatores de risco, classificação clínica, e o potencial sinérgico das estratégias de terapêutica combinadas.

MÉTODOS: Foi efetuada uma pesquisa da literatura existente na base de dados bibliográfica *PubMed*, utilizando os *Medical Subject Headings* "onychomycosis" e "therapeutics". Duzentos e vinte e seis artigos foram selecionados, compilados em categorias e analisados. Foram efetuadas pesquisas suplementares de acordo com as categorias identificadas.

DISCUSSÃO: Os tratamentos emergentes incluem novos fármacos tópicos, terapêutica fotodinâmica e com laser, e ainda a utilização de iontoforese e de ultrassom como facilitadores da penetração dos agentes tópicos. Relativamente aos novos fármacos tópicos, o tavaborole e o efinaconazol mostram potencial acrescido pelas capacidades aumentadas de penetração ungueal. O laser de CO_2 fracionado e o laser Nd:YAG revelam resultados promissores quando utilizados em conjunto com a terapêutica sistémica ou tópica. A eficácia de tratamentos precedentes, como métodos de desbridamento ungueal químicos ou físicos, também merecem investigação adicional. Por último, a eliminação de reservatórios fúngicos com aparelhos de higienização utilizando raios ultravioleta poderá ter um papel importante na redução da taxa de reinfeção.

CONCLUSÃO: O desenvolvimento das novas tecnologias é promissor particularmente quando contraindicada a terapêutica sistémica. Por outro lado, a implementação de tratamentos combinados, dentro do leque aumentado de opções disponíveis no momento, tem demonstrado eficácia na resolução desta patologia.

ABSTRACT

BACKGROUND: Onychomycosis is a fungal infection of the nail unit which presents a therapeutic challenge for practitioners and patients alike. Affecting approximately 10% of the general population, this condition is characterised by discouraging cure rates, extensive treatment regimens, and notoriously high relapse rates; creating a great incentive for new and improved therapeutic options in this area. Current treatment options include lengthy courses of systemic antifungals, and long-term application of topical lacquers, both of which struggle to penetrate the formidable nail barrier. The former are associated with numerous drug-drug interferences and adverse effects, rendering them often unusable in the aging polypharmacy population amongst which these infections are increasingly prevalent. The latter require meticulous patient compliance, and are recommended solely for mild to moderate cases, where they provide limited success nevertheless. In light of these realities, it is prudent to discuss the role of new treatment modalities and the valuable improvement in efficacy and quality of life which they may bring.

OBJECTIVES: This review of literature aims to display and summarise currently prevalent treatment options alongside novel modalities which show promising results and merit further investigation. A complete approach to onychomycosis is exposed from diagnosis to treatment, including mention of risk factors, aspects of clinical classification, and discussion of the synergistic potential behind combined strategies of treatment.

METHODS: A search of the existing literature concerning the *Medical Subject Headings* "onychomycosis" and "therapeutics" was carried out using the *PubMed* database. Two hundred and twenty-six articles successfully met the search criteria and were categorised and reviewed, with supplementary searches done according to the categories identified.

DISCUSSION: Emerging treatments include new topical drugs, photodynamic and laser therapies, and complementary adjuncts such as iontophoresis and ultrasound as penetration enhancers for topical therapy. In terms of new topical drugs, both tavaborole and efinaconazole show potential due to their improved nail penetration abilities. Fractional CO_2 lasers and long-pulsed Nd:YAG show promising results in conjunction with systemic or topical therapy. The efficacy of chemical or physical debridement techniques as preliminary treatments also warrants further investigation. Lastly, preventative sanitation using ultraviolet devices could be fundamental in eliminating fungal reservoirs and reducing the rate of auto-reinfection.

CONCLUSION: It is clear that developments in modern technology have a lot to offer in the treatment of onychomycosis, particularly in patient populations with contraindications for systemic treatment. The combined implementation of this widened armamentarium is an exciting direction for therapeutics in this area.

KEY WORDS: Onychomycosis, Topical AND Systemic Therapeutics, Laser, Non-Pharmacological Treatment

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List of Abbreviations

AI	Artificial Intelligence
AIDS	Acquired Immunodeficiency Syndrome
CO_2	Carbon Dioxide
DLSO	Distal and Lateral Subungual Onychomycosis
DNA	Deoxyribonucleic Acid
DMSO	Dimethylsulfoxide
ECM	Extracellular Matrix
EO	Endonyx Onychomycosis
HIV	Human Immunodeficiency Virus
KOH	Potassium Hydroxide
LNF	Lateral Nail Fold
MAL	Methyl-Aminolevulinate
MIC	Minimum Inhibitory Concentration
MeSH	Medical Subject Headings
MOA	Mechanism of Action
NDM	Non-Dermatophyte Mould
Nd:YAG	Neodymium-doped Yttrium Aluminium Garnet
PAS	Periodic Acid Schiff
PCR	Polymerase Chain Reaction
PDT	Photodynamic Therapy
PNF	Proximal Nail Fold
PSA	Photosensitizer Agent
PSO	Proximal Subungual Onychomycosis
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
SWO	Superficial White Onychomycosis
TDO	Total Dystrophic Onychomycosis
UV	Ultraviolet
5 - ALA	5-Aminolevulinic Acid

Glossary of Terms

Arthroconidia - Small remnants of fungal hyphae which can break off and remain lodged in the nail bed.

Dermatophytoma - An accumulation of hyphae and fungal by-products beneath the nail, analogous to a cyst of hyphae.

Leukonychia - Referring to opaque white lines or patches appearing on the surface of the nail.

Onychogryphosis - A hypertrophic state of the nail that may resemble a ram's horn.

Onycholysis - The separation of the nail plate from the nail bed.

Onychophagia - Referring to the habit of fingernail biting.

Paronychia - Inflammation of the nail folds.

Subungual Hyperkeratosis - A disorder in which there is excessive reproduction of keratin and/or fungal material, accumulating between the nail plate and nail bed.

Introduction

Onychomycosis is a common fungal infection of the nails which poses a therapeutic challenge for both practitioners and patients. Current pharmacologic treatment options struggle to penetrate the nail barrier, and the slow-growing nature of this appendage demands lengthy treatment regimens before visible results are seen. With a growing prevalence amongst the elderly fringe of society, most of whom rely on the cocktail of systemic drugs characteristic of geriatrics, systemic treatment can often be contraindicated. Unfortunately, topical lacquers offer disappointing cure rates, and require a sustained level of patient compliance which can often be unrealistic. Pre-treatment interventions with chemical or physical debridement agents are a promising addition to the therapeutic algorithm, priming the nail surface for enhanced penetration of treatment. Additionally, newer modalities including lasers and photodynamic therapy, could provide a much needed resource for increasing cure rates, whilst side-stepping the need for systemic drugs and potentially decreasing treatment length. Taking into consideration these new realities, this study aims to provide a succinct exposition of the current state of knowledge concerning onychomycosis, covering clinical classification, diagnostic methods, and exploring present and upcoming pharmacological and non-pharmacological treatments.

Methodology

A literature search was carried out using the PubMed library, restricted to literature published between January 2001 and December 2021, and applying the following *Medical Subject Headings*: “onychomycosis” AND “therapeutics”. Advanced search filters were used to select original studies, classical reviews, and systematic reviews, written in English and Portuguese, and excluding veterinary studies.

This search resulted in 341 articles. After a preliminary reading of titles and their abstracts, 115 articles were excluded - for relating to niche population groups, particular clinical cases, or unavailability of the article. The remaining 226 articles were sorted into multiple categories according to their themes, including diagnosis techniques, treatment type (topical, systemic or physical enhancement) and active component. Strategies for treatment were listed and analysed accordingly and were subsequently used to construct an index of topics. Emphasis was given to studies exploring novel treatment techniques, and supplementary searches were carried out using the original key words + the strategy terms previously categorised (e.g. “onychomycosis + photodynamic therapy”). The bibliographies of the reviewed literature articles were consulted and additional relevant citations were referenced within the text or used to construct summary tables.

See supplementary file 1.

Discussion

Epidemiology

Onychomycoses is one of the most common causes of nail pathology and makes up 30% of all fungal infections.[1] Various epidemiological studies have been undertaken in different countries and continents over the years to estimate the prevalence of onychomycosis within society. These studies are influenced by how the sample is sourced (whether or not pre-existing nail changes were used as entry criteria) and the method used to confirm infection. Project Achilles, one of the largest European studies on onychomycosis, estimated the prevalence to be 26% in the general population, which translates roughly to 2 out of every 10 patients.[1,2] Various researchers have made observations on the possible impact of native meteorological conditions, as well as local footwear habits and exposure to damp communal environments (e.g. sauna in Finland).[3]

See Table I

Anatomical Structure of the Nail Unit

The point of entry of the infectious agent with regard to the nail is the main characteristic utilized in classifying onychomycosis infections, and so it is worthwhile to review the anatomical composition of the nail unit before approaching classification. This review may also help to understand the role of the different risk factors involved.

The nail unit is made up of the matrix, eponychium, cuticle, lunula, proximal and lateral folds (PNL, LNF), nail plate, nail bed and hyponychium. Growth begins at the nail matrix, a concentration of cells located beneath the PNL, which generates the cells that keratinize and are pushed distally, becoming the nail plate. Under the PNF lies the eponychium, a band of cells which produce the cuticle. The cuticle is a keratinized layer of stratum corneum that stretches over the newly grown nail plate, creating a seal over the PNF, thus preventing water and yeast invasion. The lunula is the distal part of the matrix, visible as a lighter crescent shape. [4,5]

The nail plate is composed of layers of compacted keratin which confer strength and flexibility. It is avascular and non-innervated and depends on its strong attachment to the nail bed for nutrient supply. The shape and size is determined by the structure of the underlying distal

phalanges, whereas the colour results from the capillaries present in the highly vascularized nail bed below. [4,5]

The nail bed extends distally, developing into the hyponychium as it reaches the free edge, where the keratinizing cells detach themselves. The seal formed by the attachment of the hyponychium to the underside of the nail plate is called the onychodermal band. The PNF and LNFs are cutaneous barriers which border the periphery of the nail plate, together known as the paronychium.[4,5]

See Fig. 1

Causative Organisms

Onychomycosis infections originate from dermatophyte and non-dermatophyte fungi, as well as from the yeast species *Candida*. Dermatophyte infections of the nail are commonly referred to as *tinea unguium*; these fungi from the athrodermataceae family, obtain nutrients via keratinolytic proteases, and are the most frequently identified organisms in onychomycosis.[6] *Trichophyton interdigitale* and *Trichophyton rubrum* are responsible for the majority of cases;, whilst other fungi of the *Trichophyton* species and *Athroderma* and *Epidermophyton* genus make up the minority. Non-dermatophyte moulds (NDMs) including *Scopulariopsis spp.*, *Aspergillus spp*., *Fusarium spp*., and *Acremonium spp*., are not keratin-oriented but may still infect nails due to their saprophytic nature.[7] These are hyaline and dematiaceous filamentous fungi commonly isolated as soil saprophytes or plant pathogens.[7] The hyaline septate hyphae colonize the surface of the nails and grow in a radial manner, causing structural damage to the nail without entering living tissue. They are sometimes considered as secondary invaders as they feed off the unkeratinized intercellular cement, taking advantage of keratin destruction by previous trauma, infection or nail disease.[8] This may explain why they most commonly affect the toenails rather than fingernails, these being more prone to traumatic occurences.[9]

Yeasts from the *Candida* species make up the third class of responsible agents of which *C. albicans* is the most commonly identified. *Candida* primarily affects fingernails and is estimated to be responsible for 70% of fingernail onychomycosis.[10,11,12] The prevalence of the different agents varies between geographical locations, with dermatophytes being the most commonly identified within Europe, and yeasts taking the lead in Africa.

Role of Biofilms

Formation of fungal biofilms has been proposed as one of the mechanisms responsible for the high resistance rates of onychomycosis. Besides being planktonic organisms – meaning they can exist individually in the environment – fungi can form complex arrangements known as biofilms.[13] These consist of sessile microbial communities encased within an extracellular matrix (ECM), which can strongly attach to epithelial surfaces, such as the nail plate. The ECM creates a protective barrier, providing shelter from host defences and antifungals, and creates a platform for inter-fungal communication and metabolic cooperation.[14] The biofilm acts as a persistent source of reinfection and increased virulence, explaining in part the difficulties surrounding onychomycosis treatment and the high rate of recurrence.

See Table II

Risk Factors and High Risk Populations

Age

The incidence of onychomycosis increases in correlation with age, with the highest frequency amongst the elderly population.[15] This association may be explained by age related deterioration of the peripheral circulation and immune system, and the increased incidence of comorbidities such as diabetes, obesity, malignant disease, primary or acquired immunodeficiencies, or the requirement of immunosuppressive therapy. Additionally, the speed of nail growth slows down with age, with nails often becoming thicker, ridged and more brittle.[16,17] Elderly individuals may also have physical difficulties with carrying out optimal personal foot hygiene.[18] The influence of age on drug metabolism and distribution also makes for a poorer response to treatment. Furthermore, polymerisation in poly-medicated elderly individuals and the drug-drug interactions which ensue, often compromise the choice of treatment.[19]

Gender

Onychomycosis is significantly more common in men than in women.[20] Studies have indicated that the disparity between genders may involve differences in endogenous hormone levels, as progesterone can inhibit dermatophyte growth, improving treatment response.[21]

Occupation and Water Exposure

Individuals who carry out domestic wet work and have increased exposure to water-based activities, have a superior susceptibility to onychomycosis, particularly of the fingernails.[22] During

the previous decades, housework has been stereotypically a women's responsibility, and thus the female population was mostly faced with this exposure and subsequent risk. At present, the paradigm shift in the division of domestic labour has altered the stereotype, meaning wet work related risk should no longer be defined by gender.[23] Furthermore, the evolution and accessibility of modern domestic technologies including dishwashers and laundry machines, has significantly decreased the necessity for hands-on wet work.

Other professions such as fishermen, fishmongers, florists, and swimmers (amateur and professional), also suffer a higher prevalence of onychomycosis. Notably, these vocations share the common factor of increased contact with water.[24]

Diabetes

Various studies have shown an increased prevalence of onychomycosis in the diabetic population, which may be explained by changes in micro and macrovasculature, as well as compromised wound healing. An infected and thickened toenail is more than just a cosmetic issue, as the nail deformity can create abnormal pressure points, increasing the risk of developing diabetic foot ulcers. These can progress into cellulitis and/or osteomyelitis, and ultimately require limb amputation. [25,26,27,28]

Psoriasis

The incidence of onychomycosis in psoriatic patients is greater than in the general population.[29] Psoriatic nails can suffer from multiple clinical alterations, including subungual hyperkeratosis, onycholysis and brittleness, which create an environment more susceptible to infection, besides mimicking onychomycosis and complicating diagnosis.[30,31]

See Table III

Clinical Classification

Classification systems for onychomycosis are based on the entry point of the infectious agent, the pathway it takes, and the subsequent pattern produced on the nail plate.[32] Newer classifications have taken into account aetiology and end stage infections. Currently, five clinical types are recognised: distal and lateral subungual, superficial white, proximal subungual, endonyx, and total dystrophic. Clinical classification provides a basis for therapeutic decision-making, often predicting the most probable causative agent.

Distal and Lateral Subungual Onychomycosis

Distal and lateral subungual onychomycosis (DLSO) is the most prevalent form of infection; beginning distally at the hyponychium and progressing proximally via the LNF until it reaches the matrix.[32] DLSO infections are most prevalent on the toenails, and are clinically characterised by subungual hyperkeratosis, white or yellow toned dyschromia, and onycholysis.[33] Dermatophytoma is a frequent complication of this subtype which impedes the reachability of systemic treatment, often demanding surgical excision or chemical abrasion.[34,35] The most commonly isolated agents are *T. rubrum* and others of the *trichophyton* species, although NDMs and *Candida spp*. may likewise be responsible.[36,37]

Superficial White Onychomycosis

In superficial white onychomycosis (SWO), the clinical pattern begins on the dorsal surface of the nail plate, with fungal invasion of the upper layers of keratin. It is most commonly caused by *T. interdigitale* and *T.rubrum,* and less frequently by *Acremonium spp., Aspergillus spp., Fusarium spp* and other NDMs.[38] Visually, SWO can present as friable patches of white discolouration, or transverse striae of leukonychia, across the surface of the nail.[39] Long-term infections can progress with deeper penetration, particularly those by NDMs; this is potentially explained by the eroding bodies which they possess.[40,41] Alternative colourations have also been described, such as black superficial onychomycosis, where *Aspergillus niger* and *Neoscytalidium spp.* are isolated; in these cases, differential diagnosis with melanoma is required.[35,42,43] SWO occurs primarily in the toenails and frequently affects multiple nails.[33] Additionally, cases have been described where both SWO and DLSO are simultaneously present on the same nail.

Proximal Subungual Onychomycosis

Beginning with a proximal invasion via the cuticle area, proximal subungual onychomycosis (PSO) is a slightly less common class of infection. This subtype is predominantly identified in immunocompromised individuals, and was historically a pathognomonic sign of AIDS.[44,45] The infection spreads distally under the nail plate, as the affected nail matrix grows out.[33] Visual changes to the nail plate include leukonychia in patches or striated bands - which can be transverse or longitudinal- , subungual hyperkeratosis, proximal onycholysis, and general destruction of the nail plate.[34] PSO is most commonly linked to NDM species like *Fusarium spp.* and *Aspergillus spp.,* and dermatophytes such as *T. rubrum*.[46,47] Periungual inflammation is almost always present when NDMs are responsible.[48]

Endonyx Onychomycosis

Endonyx onychomycosis (EO) was initially classified as a sub-type of DLSO, as both originate distally. Etymologically, the term endonyx refers to the deeper layers of the nail plate, reflecting the characteristic invasion of the interior layers of the nail. Clinically, it is distinguished from DLSO by the absence of inflammation of the nail bed or subungual hyperkeratosis; the nail plate remains firmly attached without onycholyis.[49] Other characteristics include leukonychia and lamellar splitting of the nail, which creates friable layers.[49,50] The causative agents associated also differ, with *T. soudanense* and *T. violaceum* being predominantly responsible for EO, as opposed to *T. rubrum*, the primary culprit in DLSO (although *T. rubrum* EO has also been documented).[49] The location of the fungal elements within the interior layers of the nail makes treatment particularly difficult.[51]

Total Dystrophic Onychomycosis

Total dystrophic onychomycosis (TDO) denotes the end-stage of nail plate invasion, where the entire thickness of the nail plate is affected, reaching the nail bed and matrix. Primary TDO most often develops in cases of chronic mucocutaneous candidiasis, diagnosed in HIV patients or in the context of primary immunodeficiencies.[12] TDO can result from any of the aforementioned subtypes but is most commonly preceded by DLSO and PSO, and *T. rubrum* is the most frequently identified organism.[34] Clinically, the nail unit is characteristically thickened and covered with fungal elements, with friable, crumbling portions usually present.

See Tables IV, V and Fig. 2

Diagnosis

Although the clinical appearance of the nail can offer some clues towards the most likely agent involved, these associations are not definitive, and the same organism can produce various presentations. Most clinical nail signs have multiple aetiologies and therefore mycological analysis is fundamental in avoiding inefficient treatments and incorrect diagnosis.[52,53,54] Fungal identification is also beneficial with regard to choosing therapeutic management, as particular drugs or preparations may be indicated against certain organisms or subtypes. Despite this reasoning, empiric treatment continues to be highly implemented.[55]

Diagnostic methods include: direct microscopy, culture, histopathology and molecular biology. To ensure clinically significant results, systemic antifungal treatment should be suspended three months prior to specimen collection, and topical treatment 2 to 4 weeks prior, as the presence of remaining antifungals can inhibit culture growth. Similarly, proper specimen collection is essential; samples should be carried out with sterile clippers and/or curette blades, and avoid collecting external contaminants present distally.[11] Preparation should involve cleansing with alcohol and removal of hyperkeratotic matter to partially expose the affected nail bed.[56] The clinical sub-type of onychomycosis determines the preferred site of sample collection and the type of sample required.[56,57]

See Table VI

Dermoscopy

Nail plate dermoscopy is a non-invasive technique capable of differentiating between onychomycosis, traumatic onycholysis and melanonychia. A positive onychomycosis diagnosis is suggested by jagged proximal edges and polychromatic longitudinal striae in the area of onycholysis, resembling the aurora borealis. Regions of hyperkeratosis manifest with a "ruined" appearance, and melanin producing fungi present a homogenous brown pigmentation, in the absence of melanin granules.[58,59] Dermoscopy can be used prior to direct microscopy to help select adequate regions for sampling.[60,61]

Direct Microscopy

Direct microscopy utilizes potassium hydroxide (KOH 10-20%) and an optical microscope. The KOH dissolves the keratin structure of the nail plate, leaving behind fungal hyphae if these are present.[62] This method is one of the most efficient as it can be carried out in-office in minutes, however, it has low sensibility. The reliability of the interpretation depends on the experience of the technician and on the quality of the sample collected. Furthermore, optic microscopy is unable to identify the species responsible, or yet establish the viability of the fungi. Chicago blue sky added to the preparation can improve visibility of hyphae and spores, increasing sensibility and pushing specificity above 90%, without compromising on speed.[63,64] Alternative colorations with higher specificity include counterstaining with chlorazol black, which marks fungal hyphae, or fluorescent microscopy with calcofluor white, which stains the chitin contained within the fungal cell wall. However, these are less available in office as they require more specialized microscopes. [53,11,65]

Fungal Culture

Fungal culture remains the only technique capable of identifying any organism responsible and verifying its viability, thus it is considered the gold-standard diagnostic method. Samples should be sent for culture irrespective of the results of direct microscopy, as lack of visual observation does not fully exclude the diagnosis. Different culture mediums are required to provide for the various species of fungi. Unfortunately, culturing is a lengthy process, with NDMs taking 1 week and dermatophytes requiring at least 2; a standard time-frame of 4 weeks is usually implemented, with a false-negative rate of 20-35%.[11,66] Cultures are considered pathogenic upfront if dermatophytes are identified; yeasts and other NDM cultures however, demand identification of hyphae, spores, or yeast-like cells on previous direct microscopy to be considered significant. Conclusive confirmation of NDMs requires 3 consecutive isolations of the agent within 1-2 week intervals, without simultaneous growth of dermatophytes. It is important to note that cases of co-infection are increasingly being reported and pose a unique diagnostic and therapeutic challenge, often requiring repeat sampling techniques, as one agent can mask the growth of the other.[66,67]

Histopathology

Histopathological analysis utilizes nail plate clippings which are embedded in paraffin wax, sectioned into thin slices, and stained with Periodic Acid Schiff (PAS), before being microscopically analysed; this stain is able to identify glycogen and mucoproteins in the fungal cell wall and is more sensitive than KOH preparation and culture alone. Hence, histopathology is often referred to in patients with previously negative diagnostic exams – despite a high level of suspicion – and has a role in eliminating differential diagnoses. Similar to direct microscopy, it is unable to identify the species or viability of the organisms encountered.[68,69]

Polymerase Chain Reaction Assay

Lastly, Polymerase Chain Reaction (PCR) amplification of fungal DNA fragments is a speedy method of diagnosis offering a high level of specificity, for an equally high price point, which unfortunately renders it unsuitable for everyday practice. At the moment, PCR assay is only capable of identifying *T. rubrum*, and is unable to assess viability.[56,70]

Artificial Intelligence

More recently, artificial intelligence (AI) algorithms have been developed for onychomycosis, with studies showing competitive diagnostic accuracy when compared with dermoscopy and observation by experienced dermatologists.[71] These tools could potentially serve

as gate-keeping methods to more costly lab-based techniques, aiding primary care physicians in their clinical decision-making. AI also has a role in improving literacy in healthcare, offering patients a valid diagnostic tool for their own use, before resorting to healthcare services.[41,71,72]

See Table VII

Treatment

The objective of onychomycosis treatment is to eliminate the fungal organisms responsible and return the nail to a healthy state. For results to become visible, the cured nail must grow out; with fingernails growing 2-3 mm per month and toenails 1-2mm per month, this can be a year long ordeal.[73] Complete remission and recovered nail unit structure is notoriously difficult to achieve, particularly in cases of severe onychomycosis (TDO) or those which are secondary to risk factors.[74] Identification of the causative organism prior to treatment avoids unnecessary medication, risks associated with concomitant drug exposure, and the financial burden inherent to the long-term nature of onychomycosis.[75]

Factors which influence treatment outcome include patient adherence, the bioavailability of the drug, the virulence of the fungal strain, and pharmacological interactions with pre-existing prescriptions. Besides the importance of choosing appropriate antifungal drugs, treatment plans should be personalized based on the degree of infection, clinical subtype, the organism responsible (if identified), and the patient's current medication and overall preference. Various regimens are currently available including oral/systemic antifungals, topical solutions, laser and photodynamic therapy, and in extreme cases, surgical avulsion as a complement to standard treatment.[76]

Rationale for Treating

Despite not being a life-threatening condition, onychomycosis can have a significant impact on patients' quality of life (QoL), interfering with physical, functional, psychosocial and emotional aspects. Patients describe difficulties in cutting nails, pain or discomfort with certain footwear, and feelings of embarrassment and aesthetic disfigurement, particularly in social situations involving display of the feet.[77,78] Preoccupation concerning the spread of the infection to other nails, or to other people, is also described. Female patients generally score lower on QoL scales than men in relation to toenail but not fingernail infections.[78] Treatment of onychomycosis is necessary not only for health reasons, but also to improve QoL. Untreated infections can progress to complete destruction of the nail plate, ingrown nails, or secondary infections, particularly in high risk patients, and even spread to glabrous skin or the groin area.[79,80]

Basis of Pharmacological Therapy

Most agents utilized against onychomycosis have a mechanism of action (MOA) based on inhibiting the synthesis of ergosterol, an essential component of fungal cell membranes, comparable to mammalian cholesterol.[81] Ergosterol biosynthesis involves a multi-step pathway dependent on several enzymes, all of which can be targeted by antifungal drugs.[82,83]

See Fig. 3

Systemic Treatment

Systemic agents used include the allylamine terbinafine, and the azoles itraconazole and fluconazole. Systemic therapy is recommended for any diagnosed onychomycosis, and is particularly indicated when large areas of the nail are involved, multiple nails are affected, infection reaches the nail matrix, or in the presence of dermatophytoma.[84] Systemic treatment is generally established as the most effective mode of action, as a result of its ability to penetrate the nail unit - including the nail bed, matrix, PNF and LNFs - via the reticular circulation of the digit. Effective plasma concentrations are typically reached within 3 weeks and ungual infiltration is present within 7 days. Upon discontinuation, ungual drug concentrations can remain for months, despite plasma levels decreasing rapidly. Additionally, these regimens have a shorter duration and score higher cure rates compared with topical therapy.[85] However, the risk of drug-drug interactions and hepatotoxicity renders them less suitable in polypharmacy patients, with particular care required when prescribing to patients with diabetes mellitus, liver disease, or in immunocompromised individuals.[86]

Terbinafine

Terbinafine is a synthetic allylamine derivative with fungicidal properties, effective against dermatophyte, NDM and mixed origin onychomycosis. Studies prove it to be amongst the most successful treatment options, and it is the most commonly prescribed within Europe and North America.[87] Its MOA blocks ergosterol synthesis by inhibiting fungal squalene epoxidase, generating a build-up of toxic levels of squalene as a by-product, thus possessing both fungistatic and fungicidal properties.[88] The typical dose is 250mg once daily for a total of 6 weeks in fingernail infections, and 12 weeks in toenails.[88] Alternative pulsed dosing regimens (500mg daily for a week, followed by an interval of 3 weeks, repeated twice in fingernails and thrice in toenails) have not proven more effective than continuous dosing. With a mycological cure rate of 76% and a clinical cure rate of 66%, terbinafine is the highest scoring systemic option.[62,89] Its bioavailability is 70-80% and

maximum plasma concentration is reached within 8 hours. Absorption is not affected by ingestion of food or by acidic pH. Fungicidal concentrations remain present in the skin, hair and nails 15 to 20 days after cessation of treatment, conferring a long-term effect which persists after discontinuation. Common adverse effects occur in up to 10.5% of patients and include gastrointestinal disturbances, headache, altered taste perception, rash, photosensitivity and subacute cutaneous lupus erythematosus.[90,91] Terbinafine offers minimal drug interactions when compared with azole options, and a higher safety profile.[92]

The Azoles

The azoles itraconazole and fluconazole, are fungistatic compounds which interfere with ergosterol formation by inhibiting fungal cytochrome P-450. This disrupts the production of vital sterols, compromising the permeability of the cell membrane and leaving fungi vulnerable to osmotic damage and phagocytosis. The accumulation of un-metabolized ergosterol precursors is also though to play a role.

Azole molecules contain a lipophilic tail which binds to the fungal cytochrome; the more lipophilic, the greater the selectivity for the fungal cytochrome and higher the affinity for binding. Just as their MOA interferes with fungal cytochrome P-450, it can also affect the human cytochrome P-450 isoenzymes involved in the metabolism of other drugs. This interaction is responsible for a plethora of drug-drug reactions including but not limited to: antihistamines, anti-microbials, anti-retrovirals, chemotherapy drugs, steroids, barbiturates, cardiovascular drugs, psychotropic actives and oral contraceptive agents.[93] Any drug metabolized by this cytochrome can potentially be affected by azole therapy; therefore, careful assessment is required before utilizing actives from this class, and certain combinations demand supervision of drug levels and liver enzymes. Between itraconazole and fluconazole, the former presents the highest affinity for the fungal cytochrome, reducing the occurrence of drug interactions. Previously, ketoconazole has also been prescribed, however, due to a high risk of hepatotoxicity, it is no longer utilized.[94]

Itraconazole

Itraconazole has a broad spectrum of activity against dermatophytes, NDMs and yeasts, and is mainly considered when patients have reacted adversely to oral terbinafine, or when harder to treat NDMs or yeasts are implicated.[95] Mycological cure rates range from 63% to 69%, and complete cure rates between 21% to 22%.[96] Itraconazole has an oral availability of 55% and peak plasma concentrations are reached within 2-5 hours. Due to its high affinity for keratin, the drug then accumulates within the nail plate, and remains detectable for 6 to 9 months after

discontinuation, supporting the efficacy of pulse regimens which take advantage of this reservoir effect.[97]

Regarding itraconazole, continuous treatment is recommended for toenail onychomycosis, using 200mg per day for 12 weeks. In fingernails, pulse dosing is indicated, with 200mg taken twice a day for 1 week followed by a no treatment period of 3 weeks, repeated twice for a total of 8 weeks (three repetitions can be used for toenails). In both cases, doses should be administered with meals for increased bioavailability.[98,99] Pulse regimens have a lower risk profile, are more cost-effective, and show slightly higher mycological and clinical cure rates when compared with continuous administration.[100,101] Common side effects include headaches, gastrointestinal discomfort, raised triglycerides levels and hepatic dysfunction. With continuous treatment, liver function should be monitored to prevent hepatic toxicity.[102] Additionally, itraconazole has been associated with adverse cardiovascular events and should be avoided in patients with congestive heart failure; cardiac workup is prudent in high risk patients.[103]

Fluconazole

Also belonging to the azole class, fluconazole is effective against dermatophytes and yeasts, and is the treatment of choice against *Candida* onychomycosis. With mycological and clinical cure rates of 61.7%, and 46.7% respectively, fluconazole does not perform as well as terbinafine or itraconazole, and thus is called upon when these are contraindicated.[104,105] Due to its extensive plasma half-life (20-50 hours), administration can be done in longer intervals, with typical regimens consisting of 150mg doses given once per week, for 12 to 24 weeks in fingernail infections, and 24 to 48 weeks in toenails, or until the affected nail has grown out.[105,106] The drug remains present in the nail plate for up to 5 months after cessation of treatment. Adverse effects include gastrointestinal upset, headache, skin rashes and insomnia. Again, liver function testing is recommended prior to initiating treatment and at regular intervals throughout.[105]

See Table VIII

Topical Treatment

The use of topical agents is limited by the challenge of effectively permeating the nail plate, with relapses and re-infection occurring in approximately 25% of cases.[107,108] Formulations have been revised over time to increase their permeation ability, sometimes incorporating vehicles for improved transungual delivery.

Various elements influence drug transport into the nail plate, including the physicochemical properties of the molecule such as size, shape, charge and hydrophobicity. Factors which increase ungual penetration include low molecular weight, increased polarity, and low affinity for lipids.[109] Although lipophilic drugs are able to penetrate to a degree by binding to keratin, counterproductively they become inactive once they have bound. In chronic onychomycosis, structural changes to the nail create a more tortuous porous network which is adverse to penetration, however, small hydrophilic molecules may have an advantage. Thus, an ideal topical active should have a low affinity for keratin, and should be used early on in the disease.[110] The hydration of the nail itself also predicts the interactions between the keratin network and the permeating drug.[111] Lastly, formulation characteristics such as drug concentration and pH must be considered.

Nail lacquers are typically used once daily or once weekly (depending on the active drug), and should be applied to the whole affected nail plate, including the nail under-surface if exposed. Once dried, a film of residue remains on the surface, acting as a drug reservoir.[112] This coating keeps the drug in contact with the nail and has the added benefit of limiting the adhesion of other fungal propagules, thus preventing reinfection. It also maintains the nail plate hydrated, facilitating drug diffusion.[111] Currently, topical lacquers are indicated for the treatment of SWO and early cases of DLSO where less than half of the distal nail is affected, or when removeable areas of onycholysis are present.[113] They are also used when systemic treatment cannot be tolerated by the patient. Topical drugs categories include amorolfine, ciclopirox, and the newer tavaborole and efinaconazole.

Amorolfine

Belonging to the morpholine class, amorolfine is a fungistatic and fungicidal molecule, whose MOA inhibits ergosterol synthesis at two separate points.[112] It is effective against dermatophytes, yeasts and NDMs, and is recommended for SWO and mild cases of DLSO affecting up to 2 nails, without matrix involvement.[114] Following application, amorolfine rapidly penetrates the nail plate and active concentration levels are maintained for several days; typical regimes require once or twice weekly application for 24 weeks in fingernail infections and 36 - 48 weeks in toenails.[115] Adverse effects are minimal, including local irritation, itching, redness and burning sensation.[116] In severe cases, combined treatment with oral itraconazole or terbinafine can offer superior cure rates.[117–119]

Ciclopirox

From the hydroxypyridone class, ciclopirox is a fungistatic and fungicidal drug which inhibits essential enzymes for fungal metabolic processes. This involves chelation of Fe^{3+} and Al^{3+} cations, which obstructs metal dependent enzymes otherwise responsible for eliminating peroxides within the fungal cell. Topical ciclopirox solution is a broad-spectrum option particularly effective against yeasts, and can be used in can be used in cases of SWO and mild to moderate DLSO without lunula or matrix involvement.[120] Typical treatment requires daily application over 48 weeks, though adaptations can be made depending on the location of the infection (24 to 36 weeks for fingernails, and 36 to 48 weeks for toenails). The solvent component of the 8% lacquer evaporates once the solution is applied to the nail, increasing the concentration of the active ingredient to 34.8%. The lacquer should be applied atop the previous coat, with an alcohol cleanse once per week to remove excess build-up. Adverse effects are uncommon, but include local pruritus and burning sensation.[122]

Tavaborole

The first member of a new category of boron based, low-molecular weight and water-soluble antifungals, tavaborole is a fungistatic drug available as a 5% topical solution. Its unique MOA interrupts protein synthesis within the fungal cells by binding to the editing site of aminoacyl-transfer RNA synthetases, ultimately supressing fungal activity. Tavaborole possesses a high level of nail penetration even in the presence of keratin – in vitro studies show a penetration 40 times greater than ciclopirox after 2 weeks.[124,125] Adverse effects such as localised skin exfoliation, erythema and dermatitis are reported in some patients.[124] Treatment requires daily application over a period of 48 weeks for toenails; specifications for fingernail treatment have not yet been outlined.[124,126,127] Curiously, the presence of cosmetic nail polish does not hinder the transungual penetration of the drug, and may even have an enhancing effect.[131]

Efinaconazole

Developed specifically for the treatment of mild to moderate DLSO, efinaconazole solution is a triazole antifungal effective against dermatophytes, NDMs and *Candida*, with cure rates comparable to systemic itraconazole.[129,130] As with the systemic azoles, efinaconazole inhibits ergosterol synthesis, causing destruction of the fungal cell wall. It is able to penetrate the nail plate without requiring physical debridement due to its small molecular weight and hydrophilic properties which make it less keratin-binding.[131] Clinical trials have observed mild side-effects such as local erythema, dermatitis, and vesicle formation at the site of application. Research so far has concentrated on the use of efinaconazole for toenail onychomycosis, with a standard course of

treatment requiring daily application over 48 weeks.[130,132] Similarly to tavaborole, efinaconazole permeation does not appear to be affected by the presence of cosmetic nail polish.[128]

New and Upcoming Pharmacological Treatments

Several new azoles are currently under investigation as both oral and topical treatments. Voriconazole is a pre-existing antifungal with indications other than onychomycosis presently being studied for use in this area. Two case reports have shown that oral voriconazole (200mg twice daily for 12 weeks) is effective against resistant fingernail onychomycosis, and has a broad spectrum of activity, however, it is available exclusively for in-hospital use.[133] An oral ravuconazole prodrug (BFE1224) is also being investigated, and is currently undergoing phase III clinical trials.[134] Luliconazole is a fungistatic and fungicidal imidazole with promising results, undergoing phase III trials as a topical solution for severe DLSO.[28,135]

See Table IX

Nail Plate Debridement Techniques

Thickened and hyperkeratotic nail plates are a challenge against the penetration of topical and systemic drugs, often preventing the build-up of minimum inhibitory concentrations (MIC), and consequently decreasing treatment efficacy. A healthy nail plate is made up of 80 to 90 layers of keratin with an average thickness between 0.25 and 0.6mm; it is considered abnormal when it surpasses 2mm.[136,] In these circumstances, adjunctive chemical or physical debridement can lessen the distance between the active ingredient and the fungal cells, increasing treatment efficiency, and decreasing the duration of posterior treatments.[138] These measures are of particular benefit in cases of TDO with poor response to treatment, or where dermatophytomas are present.[137] Various options exist including mechanical debridement, chemical avulsion, physical treatments such as laser and light therapies, as well as partial or complete surgical avulsion.[139]

Mechanical Debridement

The simplest and oldest approach is mechanical debridement. Filing down the thick keratin nail plate is a straightforward way of minimizing this barrier against topical therapy, using a coarse nail file, sandpaper, or an electric rotary file. By reducing the critical fungal mass and the nail thickness, it is beneficial for systemic treatment as well as increasing the permeability of topical solutions.[139,140] Mechanical abrasion is readily available, fast, economic, and minimally invasive, making it an ideal precursor and accompaniment to both topical and oral onychomycosis therapy.

Microporation

Microporation or microneedling, involves drilling small holes into the nail plate whilst sparing the nail bed. This can be accomplished using microdrills, dermarollers, or even lasers, to produce micropores on the dorsal nail surface. The resulting channels increase the surface area for permeation and additionally act as wells where active drug can settle and form sustained-release reservoirs. When done correctly, the procedure is associated with minimal pain. Bio-feedback mechanism can offer additional protection by stopping upon reaching the nail bed.[143]

Chemical Treatments

Chemical substances can be applied to the nail prior to the application of active drugs to help prepare the nail for enhanced penetration. These include thiols, water, sulphites, hydrogen peroxide, keratinase enzymes and keratolytic enhancers like urea and salicylic acid, as well as fungal hydrophobins.[144,145] Thioglycolic acid for example, can sever disulphide bonds within the keratin structure, causing the nail plate to swell and increasing the permeation flux of active drugs.[146] The physical changes caused by water are similar, and aqueous vehicles also promote ungual permeation.

Sulphite solvents such as dimethylsulfoxide (DMSO) cause conformational changes in the keratin structure by altering the lipid composition of the nail, and have a role in vehicle formation to carry active drugs.[147] Keratolytic enzymes are able to disrupt the architecture of the intercellular matrix holding the nail corneocytes together, allowing cells on the surface of the nail to detach.[148] Urea preparations at high concentrations (>10%) exert a keratolytic effect with penetration enhancing capabilities similar to salicylic acid.[149] It is though that these substances work by creating new channels or pores by which the active drugs can then travel.[150] Combined formulations, such as urea and thioglycolic acid, warrant further investigation.

Fungal hydrophobins as penetration enhancers are a promising possibility. These are water soluble, amphiphilic proteins which adhere to the nail plate and act as surfactants, reducing the surface tension of water by self-assembling within the solution, and creating a hydrophilic surface with small porous structures.[147] Non-surgical or chemical avulsion of the nail plate can be carried out in extreme cases of TDO or onychogryphosis. This is performed using a 40% urea paste combined with an antifungal cream, applied to the nail and occluded with a bandage.[138]

Acid Etching

Acid etching is a chemical process which uses tartaric or phosphoric acid gels to chemically abrade the nail. Brief applications (<90 seconds) to the dorsal nail create microporosities and surface roughness, generating an increased surface area for greater penetration, and an optimal external structure for adhesion and bonding of lacquers.[151] Pre-treatment nail etching is yet another fast and effective method which can potentiate the outcome of topical therapy.[152]

See Table X

Laser and Light Therapies and Other Physical Enhancement Methods

Light therapies and physical enhancement methods have novel applications in the treatment of onychomycosis, helping to tackle the formidable nail barrier, without systemic side effects. Examples include photodynamic therapy, various lasers, ultraviolet light, and treatments with iontophoresis and low-frequency ultrasound. These device based modalities are applied to the nail plate where they may enhance the permeation of active drugs, activate topically applied drugs, therapeutically target fungal structures, or thermally ablate fungal cells and the adjacent nail plate. Light therapies include a variety of wavelengths, in continuous and pulsed modalities, and can produce photodynamic, photothermal or photoablative effects. Many of these devices are approved for other uses, and are often present in dermatology offices, mitigating their financial burden. Despite not having formal indication for therapeutic use in onychomycosis, they are a competitive way to encourage drug permeation and their use is becoming increasingly justified in recurrent infections or where systemic therapy is contraindicated.

Photodynamic Therapy (PDT)

PDT is an in-office procedure involving a topically applied photosensitizer agent (PSA) which is selectively internalized by fungal cells, and activated by exposure to a light source. Once exposed, the PSAs absorb energy and generate reactive oxygen species within the fungal cells, initiating a therapeutic effect by selective chemical destruction of these organisms. PDT is effective against multiple agents due to its mechanical nature and the antifungal properties of the agents. Several PSAs have been trialled successfully against dermatophytes and non-dermatophytes. The most commonly used include phenothiazine dyes (methylene and toluidine blue), porphyrins, 5-aminolevulinic acid (5-ALA) and methyl-aminolevulinate (MAL).[153,154] The chemical structure and properties of the PSAs condition the extent of internalization by different fungal species, ultimately determining treatment success.[155]

PDT has the benefit of not interacting with other therapeutic agents, however, multiple treatments (3 to 12) are required for clinical results, with sessions separated by 1 to 2 week intervals. Increasing the amount of light radiation could reduce the number of sessions required, although it poses a greater risk of side effects such as transient pain and burning sensation which may be intolerable by some patients. Prior mechanical or chemical abrasion (urea 40%) can increase fungal uptake of the PSA. Further investigation is required in order to develop clinical treatment protocols for PDT, establish concrete data on its efficacy, and determine which PSAs are best suited to which fungi. Overall, PDT is a promising choice for the enhanced treatment of onychomycosis.[156]

Lasers

Laser therapies in the treatment of onychomycosis target fungal cells by dispensing short bursts of energy into the nail plate, causing rapid temperature elevation and photothermolysis of fungal microorganisms. Treatment is delivered in-office, using controlled energy levels in a pulsed modality. Allowing intervals for photothermal heat to dissipate prevents cutaneous damage or pain, however, specifics can vary amongst the different modalities.[157] Laser therapy shows good tolerance by patients when used at the correct intervals and wavelength, causing mild to no discomfort.[158–160] Adverse effects include overheating, burning sensation and mild bleeding from the nail bed, although pre-treatment measure using anaesthetic creams or cooling gels can help counteract the thermal symptoms.[161]

Several types of laser have been successfully trialled against onychomycosis, including Nd:YAG in short-pulse and long-pulse modalities, solid state titanium sapphire devices, diode lasers and ablative or fractional carbon dioxide (CO_2) lasers. Studies *in vitro* have shown that wave-lengths above 980nm can produce temperatures above 50°C, with complete impairment of fungal growth; this has been tested against dermatophytes and *Candida spp*.[162] Despite multiple successful investigations, laser systems currently have approval exclusively for cosmetic improvement with "temporary increase in clear nail". Further research using large sample sizes and control group moderation is required, to guarantee safety profiles and long-term clinical and microbiological outcomes, and determine the antimycotic mechanisms involved.[163] Additionally, comparison is needed versus traditional pharmacological treatments, and between the different laser modalities. It is also necessary to determine which clinical subtypes and agents of onychomycosis, are best suited to laser therapy.

Various parameters influence the safety and effectiveness of laser therapy, and should be described by treatment protocols. These include characteristics of the laser itself - such as

wavelength, frequency, pulse duration, spot size and energy fluency - and treatment features like duration, number of passes, number of sessions, and the length of the interval between them.[164] Nail thickness and the degree of infection also affect the outcome of treatment. Careful regulation is essential in preventing pain and damage to healthy cells.

Nd:YAG Laser

With wavelengths between 1064nm and 1444nm, Nd:YAG laser can effectively disintegrate fungal spores throughout the thickness of the nail plate and is the most researched laser option at present.[158] Long pulsed Nd:YAG is readily absorbed by the melanin present in the cytoderm of *Trichophyton* fungi, and thus may act directly on the fungal chromophore; this may explain its superior efficacy when compared with short-pulsed parameters.[165]

With mycological clearance rates rivalling those of oral terbinafine, long-pulsed Nd:YAG is a valid choice of treatment, especially in patients where pharmacological therapy is contraindicated. Combined regimens can offer increased cure rates with research showing that systemic terbinafine therapy or topical efinaconazole, combined with 24 weekly or 12 monthly laser sessions respectively, are highly effective duos.[166,167] Additionally, studies have demonstrated that Nd:YAG has some efficacy in clearing biofilms, and further investigation into this capacity presents an important focus for future research.[13,168]

CO_2 Laser

One of the first laser therapies to be trialled was CO_2 laser which at 10,600nm, thermally ablates the nail plate on application, eliminating fungal structures in the process. This laser is aggressive and can damage the tissue of the nail bed causing long-lasting pain and scarring. These side-effects render it a less favourable option, as more advanced and less invasive alternatives have emerged.[169,170]

The more modern fractional CO_2 laser, ablates small sections of the area of incidence, in a pin-point grid manner, producing microthermal zones of damage to the deeper layers of the nail. This reduced area of incidence improves safety parameters, decreasing discomfort and recovery time, whilst maintaining bacteriostatic and sterilizing effects.[169] By creating micro-pores within the nail plate, this laser can facilitate the delivery of topical actives. Studies combining fractional CO_2 with topical amorolfine or terbinafine, have attested to this co-operation, however, controlled comparison versus standard systemic therapy is required to legitimise this approach.[169,171]

Iontophoresis

Iontophoresis involves the application of a mild electrical field to the nail, with the purpose of increasing molecular transport by electrophoresis and less notably, electro-osmosis. *Ex vivo* experiments show that iontophoresis can encourage the transport of small, ionized molecules across the nail, and can be used effectively to enhance topical delivery of active drugs.[172–174] The ideal candidates are small, ionized and highly water soluble molecules. *In vivo* trials have been successful with active drugs including ciclopirox and topical terbinafine, showing a 5 to 10 fold increase in permeation when compared with passive topical application or even systemic treatment; terbinafine proved to have the highest delivery rates.[174–177] Localised 'tingling' sensation can occur, as well as skin irritation including erythema and vesicle formation.[172] By reducing the thickness of the nail, prior chemical or physical abrasion can further enhance the effects.[150] The potential of hand-held devices offered alongside topical formulations is encouraging and may allow for higher cure rates in onychomycosis.

Ultrasound

Low frequency ultrasound (20Hz – 1MHz) create waves which penetrate into body tissues, promoting cavitational effects which physically enhance transungual delivery with minimal thermal energy. The nail plate is coated with a topical active and small transducers are applied for short amounts of time (<120 seconds), significantly increasing penetration.[178] This technology is low-risk and causes little to no discomfort when used correctly in pulses and with temperature monitoring. Currently, portable ultrasound devices are approved for domiciliary use in other conditions, as such, it could be possible to apply this notion for use in conjunction with topical lacquers, increasing the efficacy of at-home treatment. Further research is needed to understand the mechanism involved, document with which actives it works best, and whether the effects are reproduceable in diseased nails.[178,179]

Ultraviolet

The germicidal and fungicidal properties of electromagnetic ultraviolet (UV) radiation have been well documented, with particular relevance to UV-C between 200 and 280nm. *In vitro* and *ex vivo* studies have shown that it can inactivate dermatophytes and effectively decrease colony growth.[180] The main setback is that these wavelengths are not able to penetrate the nail plate, and so their sterilizing effect is purely superficial and inadequate for treatment. Nevertheless, UV

devices remain a promising technology to tackle fungal reservoirs of re-infection, such as the shoes of infected individuals, and reduce transmission within shared spaces.

See Table XI

Surgical Avulsion

Surgical avulsion lies on the radical end of the spectrum, and involves releasing the nail plate from the nail bed, progressing either distally at the hyponychium, or proximally at the PNF, providing on the location of nail dystrophy. Prior local anaesthesia of the digit is required, and depending on the extent of the infection, the procedure can be partial or complete.[181] Nail avulsion is not a definitive cure, and should be parsimoniously used in severe cases of onychomycosis with significant history of recurrence, pain, or bacterial co-infection. Treatment should be combined with a systemic approach and/or follow-up topical therapy during the regeneration of the nail plate. Depending on how the infection has affected the nail matrix, new nail growth may remain dystrophic and separated from the nail bed.[182]

Combination Therapy

Onychomycosis therapy can be a challenging undertaking, requiring lengthy regimens yet still achieving mediocre cure rates, and suffering high rate of relapse and reinfection. Using multiple lines of attack by combining systemic and topical treatments is one way of increasing the probability of success. Combination strategies are beneficial for two reasons: firstly, they double the means of getting the active drug to the site of infection, and secondly, because synergy occurs between the MOA of the drugs used. Amorolfine, for example, inhibits ergosterol synthesis at different steps than the other antifungals (see Fig.3). Furthermore, antifungal activity is increased, even at lower concentrations of both drugs.[183] Current strategies involve the combination of topical amorolfine with oral terbinafine or itraconazole; both duos show superior cure rates when compared with monotherapy.[117]

Combination regimens can be administered consecutively or in parallel, the latter being more frequently implemented. Patients at higher risk of poor outcomes - such as those with comorbidities - benefit from the doubled effort of parallel therapy, whereas booster therapy is recommended in those who do not respond well to initial treatment.[117,184] The slow growth rate of toenails in particular, coupled with the high risk of re-exposure, create favourable conditions for chronic infections which frequently require multiple courses of treatment. The use of precursor

debridement techniques, and adjunctive physical therapies, could augment the therapeutic response, particularly in advanced cases.[184]

Cure Criteria

When discussing and comparing the various treatment options, it is relevant to consider the three cure criteria applied to onychomycosis: these are mycologic, clinical, and complete cure. Mycologic cure is often accepted as the main endpoint treatment goal, and implies fungal eradication and negative microscopy and culture; it is the only objective and consistently defined parameter used in clinical trials.[185,186] Clinical cure, requires the presence of a certain percentage of healthy nail plate (80-100%), however, aesthetic improvement does not equal cure from infection. Finally, complete cure encompasses the requisites of both mycologic and clinical cure.[187,188]

Cure rates determined by studies are often volatile, partly due to the lack of consistency in defining and measuring these parameters. For reference, gold-standard treatment with oral terbinafine has complete cure rates ranging from 14 to 90%, and 10% to 53% of all patients will relapse.[189] Large-scale clinical trials habitually implement the most stringent criteria, and can therefore suggest lower cure rates. Furthermore, the chronic nature of onycholysis does not lend itself well to the standardized deadlines of assessing cure used in trials and studies, as such, cure rates seen within the clinical setting are more promising. Onychomycosis trials typically evaluate endpoints 48 to 52 weeks after beginning the treatment; this is frequently insufficient, as toenails may require up to 72 weeks to fully regrow, not taking into account the slower growth rate seen in chronic diseases or old age.[190]

See Table XII

Preventing Reinfection

Many factors contribute to the high rate of re-infection seen in onychomycosis, including patient characteristics, foot hygiene, fungal mechanisms of survival, and re-exposure to persistent fungal reservoirs. Concerning patient characteristics, achieving permanent cure is particularly difficult amongst individuals with additional risk factors.[137] In terms of foot care, patients should be informed on how to maintain proper foot hygiene, and alerted to the signs and symptoms of tinea pedis, an infection that often co-exists with onychomycosis and may reduce treatment success.[27,191,192] Regarding fungal mechanisms, arthroconidia have proven to be particularly resistant to treatment and may serve as a reservoir for re-infection.[193] Fortunately, the development of innate resistance to antifungals is low amongst dermatophytes, meaning the same

drugs can be implemented sequentially.[194] As to fungal reservoirs, these can persist within the household, or in public areas such as shared shower facilities and changing rooms. Precautionary measures include avoiding walking barefoot in damp public areas, and the sterilisation of footwear and household spaces where it is common to be barefoot using antifungal sprays or UV devices.[195,196,197] Treatment of affected household members is prudent, as they can also act as fungal reservoirs and perpetuate reinfection.[198]

Conclusion

Emerging treatments for onychomycosis could help increase the cure rate of this persistent condition by advancing the development of combined algorithms of therapy, for boosted efficiency and faster results. New topical drugs tavaborole and efinaconazole offer improved penetration abilities, whilst photodynamic therapy, CO_2 and Nd:YAG lasers show promising ablative and fungicidal properties. These device based complements to topical therapy are particularly desirable for the treatment of the elderly population, amongst which onychomycosis is increasingly prevalent and in whom systemic treatment is often contraindicated. Whilst these modalities have proven to help obtain temporary clear nail growth, and even mycological cure, further large-scale randomized controlled trials are needed to validate the assistance they bring compared to existing options, and demonstrate their place in the treatment algorithm. Additionally, it would be constructive to carry out studies comparing the specificities of the different laser modalities, and how they perform against the various clinical presentations and fungal agents of onychomycosis.

Other methods of upgrading topical therapy and tackling the nail barrier include penetration enhancement with iontophoresis and ultrasound, as well as preparatory debridement techniques. Furthermore, in terms of reducing the rate of reinfection, ultraviolet mechanisms for the sterilization of fungal reservoirs could offer a much needed solution. Overall, the development of more sophisticated therapeutic algorithms, which exploit the synergism of combined treatment and implement modern advances, is a promising direction for the future of onychomycosis therapy.

Appendix

Supplementary File 1.

DATABASE SEARCH

(("onychomycosis"[MeSH Terms] OR "onychomycosis"[All Fields] OR "onychomycoses"[All Fields]) AND ("therapeutical"[All Fields] OR "therapeutically"[All Fields] OR "therapeuticals"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapeutic"[All Fields])) AND ((review[Filter] OR systematicreview[Filter]) AND (humans[Filter]) AND (2001/1:2021/12[pdat]) AND (english[Filter] OR portuguese[Filter]))

Table I: Studies Concerning the Prevalence of Onychomycosis in the General Population

MAIN AUTHOR	PUBLICATION YEAR	COUNTRY/CONTINENT		SAMPLE SIZE (N=)	INFECTION %	METHOD OF IDENTIFICATION	MOST COMMONLY IDENTIFIED RESPONSIBLE AGENT
HEIKKILÄ ET AL.[199]	1995	Finland		800	8.4%	Direct microscopy and fungal culture	*T. rubrum*
GUPTA ET AL. [200]	1997	Canada		2001	9.1%	Direct microscopy and fungal culture	*T. rubrum (63.8%)*
B. ELEWSKI; M CHARIF[20]	1997	Ohio, USA		1038	8.7%	Fungal culture	*T. rubrum (93.3% of dermatophytes)* (study only tested for dermatophytes)
GUPTA ET AL.[15]	2000	Canada		15000*	6.5%	Mycologic sampling	*T. rubrum*
ACHILLES PROJECT - E. HANEKE; D ROSEEUW[. 12]	1999 1999	Study Survey	Europe East Asia	22742 43914	26% 22%	KOH microscopy and culture growth (survey)	*T. rubrum (53.3%)* Identification of species was not carried out in the survey section of the Achilles project.
GHANNOUM ET AL. [201]	2000	North America		1832	13.8%	Direct microscopy and fungal culture	*T. rubrum (42.9%)*
GUPTA ET AL. [202]	2005	Canada		32193	6.4%	Direct microscopy and fungal culture	*T. rubrum (51.7%)*
IOANNIDOU ET AL.[22]	2006	Greece		23477	24.5%	Direct microscopy and culture	*Candida spp.** (49.1%)*
DEL PALACIO ET AL.[203]	2006	Spain		1000	2.6%	Direct microscopy and culture	*T. rubrum* (74.2%)

Table created based on an open search on "Incidence of Onychomycosis" of the PubMed database.

*Included data from original 2000 study.

** In female fingernails.

Table II: Causative Agents of Onychomycosis (not exhaustive)

Dermatophytes	Yeasts	NDMs
Trichophyton spp.	*Candida spp.*	*Acremonium spp.*
T. rubrum	*C. albicans*	*Alternaria spp.*
T. interdigitale	*C. parasilosis*	*Aspergillus spp.*
T. tonsurans	*C. guillermondii*	*Fusarium spp.*
T. soudanense	*C. tropicalis*	*Scopulariopsis spp*
T. violaceum	*C. lusitaniae*	*Scedosporium spp.*
Microsporum spp.	*C. krusei*	*Scytalidium spp.*
M. canis	*C. pelliculosa*	
M. gypseum		
M. audouinii		
Epidermophyton spp.		
E. floccosum		

Table III: Risk Factors for Onychomycosis

Individual Characteristics:	**Nail Characteristics:**
Advanced age[15]	Nail trauma
Gender[21]	Distorted nail surface
Genetic susceptibility[204,]	*Tinea pedis* infection[192]
Smoking[206]	Previous nail infection
Comorbidities and Diseases:	**Environment and Habits:**
Poor peripheral circulation (arteriopathy or venous insufficiency)[207]	Sports active
	Manual labour[191]
	Humid environments[210]
Diabetes[27]	Shared bathroom facilities[198]
Psoriasis[29,30]	Affected member in household[198]
Compromised Immune System (iatrogenic or due to disease)[208]	Compromised foot hygiene
	Occlusive footwear[205]
	Onychophagia

Table IV: Agents of Onychomycosis and their Characteristic Location of Infection

	CHARACTERISTIC LOCATION OF INFECTION	SUGGESTIVE CLINICAL HISTORY
DERMATOPHYTES	Toenails - 90% of all toenail onychomycosis[11] - 50% of all fingernail onychomycosis[11]	- Concomitant infection with tinea pedis
NON-DERMATOPHYTE MOULDS	Toenails - 1.5 - 6% of all toenail onychomycosis[11]	- History of nail trauma - Paronychia of 1 or more nails - Absence of tinea pedis
YEASTS	Fingernails	- History of paronychia

Table V: Summary of the Clinical Classification of Onychomycosis and Associated Features

TYPE	POINT OF ENTRY	DIRECTION OF SPREAD	KEY FEATURES OF APPEARANCE	VARIATIONS/ PRESENTATION/ SUBTYPES	MOST FREQUENT LOCATION	SPECIFIC RISK FACTORS	DIFFERENTIAL DIAGNOSIS	MOST COMMON CAUSATIVE ORGANISM	MOST COMMONLY RECOMMENDED TREATMENT
DISTAL AND LATERAL SUBUNGUAL ONYCHOMYCOSIS	Hyponychium and under surface of the nail	Proximally	- Subungual hyperkeratosis - Onycholysis - Paronychia - Yellow/white discolouration	- Brown/black pigmentation - Orange discoloration (If fungal melanonychia melanoides variant of *t. rubrum*, *Neoscytalidium dimidiatum* or *Aspergillus niger*[35]) - Longitudinal streaking of the nail - Dermatophytoma	One or both toenails of the hallux	- Tinea pedis[191]	- Traumatic onycholysis (symmetrical, without subungual hyperkeratosis) - Nail psoriasis – (diffuse hyperkeratosis, multiple toenails affected, other cutaneous signs of psoriasis)	- *Trichophyton spp.* - *Candida spp.* - *Scytalidium*[37]	- Systemic or combined
SUPERFICIAL WHITE ONYCHOMYCOSIS	Superficial surface of the nail plate	Proximally (dorsal nail plate to nail bed)	- Chalky white, opaque, friable patches - Transverse striae of leukonychia - Deep fungal penetration with friable areas reaching nail bed	- Black superficial onychomycosis, where *T. rubrum* and *Scytalidium spp*. are commonly isolated	Toenails	- Tinea pedis[191] - Thin nail plate	- Nail fragility due to prolonged use of nail polish - Transverse toenail leukonychia due to trauma	- Most common: *T. rubrum, T. interdigitale and Scytalidium spp,* - Less common: 5% due to NDMs: *Fusarium spp., Acremonium spp., Aspergillus spp*[40]	- Topical if mild to moderate - Systemic or combined if moderate to severe
PROXIMAL SUBUNGUAL ONYCHOMYCOSIS	Beneath the proximal nail fold, infection of the nail matrix	Distally, with growth of affected nail	- Proximal leukonychia - Transverse or longitudinal striae - Subungual hyperkeratosis - Proximal onycholysis	- Often accompanied by acute paronychia	Toenails are more frequently affected than fingernails	- Immunocompromised patients	- Paronychia - Pustular psoriasis - Secondary changes due to trauma	- NDMS: *Fusarium spp., Candida albicans, Aspergillus spp.* - *T. rubrum*	- Systemic or combined
ENDONYX ONYCHOMYCOSIS	Nail plate surface/ superficial	Exclusive to the nail plate.	- Lamellar splitting of the nail plate - Absence of subungual hyperkeratosis, onycholysis - No inflammation of the nail bed - Milky white discolouration/opacification	- Massive nail plate invasion, fungi create tunnels filled with hyphae and fungal elements throughout the entire thickness of the nail plate	-	-	-	- *T. soudanense,* - *T. violaceum,* - *T. rubrum*	- Systemic or combined - Photodynamic therapy based on methylene blue dye[154]
TOTAL DYSTROPHIC ONYCHOMYCOSIS	-	Generalised	- Thickened, dystrophic nail - Friable and crumbling - Thickened nail bed retaining fungal debris	- Penetration of the entire thickness of the nail plate, reaching the nail bed and the matrix	-	- Advanced stage of any onychomycosis subtype - Chronic mucocutaneous candidiasis - Psoriasis - Lichen planus - Eczema	-	-	- Systemic or combined

Table VI: Preferred Location of Sample Collection by Clinical Subtype

	PREFERRED AREA OF SAMPLE COLLECTION
DISTAL AND LATERAL SUBUNGUAL ONYCHOMYCOSIS	1. Removal of the affect distal/ lateral nail plate and hyperkeratosis. 2. Sample collection from the most proximal point of involvement.
PROXIMAL SUBUNGUAL ONYCHOMYCOSIS	1. Debride the affected proximal upper nail plate to expose nail bed. 2. Collect hyperkeratotic debris at sample site at nail bed near the lunula.
SUPERFICIAL WHITE ONYCHOMYCOSIS	3. Scraping of friable areas on the superficial nail plate. 4. Sample taken from deeper areas.
ENDONYX ONYCHOMYCOSIS	1. Nail clipping for histopathology and microscopy should show internal fungal growth.
TOTAL DYSTROPHIC ONYCHOMYCOSIS	5. Debride and remove distal aspects of the destroyed nail. 6. Nail clipping of proximal nail to avoid contaminants.

Table VII: Comparison of Diagnostic Methods

	POSITIVE TEST	SPECIES IDENTIFICATION	VIABILITY IDENTIFICATION	MINIMUM TIME UNTIL RESULT	SENSIBILITY	SPECIFICITY	COST
VISUAL DIAGNOSIS BY DERMATOLOGISTS	Presence of nail discoloration, subungual hyperkeratosis, onycholysis, or onychauxis	No	No	Real-time	75.3% [71]	-	$
DERMOSCOPY	Jagged proximal edge, spikes in the area of onycholysis, "ruined" appearance of hyperkeratosis, aurora borealis pattern [,59]	No	No	Real-time	86.2%[212]	33.3%[212]	$
MICROSCOPY WITH KOH STAIN	Visualisation of septate hyphae, arthroconidia, or yeast cells	No	No	Real-time/ minutes	48 – 60%[57]	38 – 78%[57]	$
HISTOPATHOLOGY WITH PAS STAIN	Visualisation of hyphae, pseudo–hyphae, spores, or yeasts	No	No	3-5 days	82 – 88%[57]	-	$$$
FUNGAL CULTURE	Growth on culture medium	Yes	Yes	2-4 weeks	60 – 65%[53]	83 – 100%[53]	$$
PCR ASSAY	Amplification of fungal DNA fragments	No (only *Trichophyton spp.*)	No (Yes if RT-PCR)	Days	87.3%[70,213]	94.3%	$$$
ARTIFICIAL INTELLIGENCE	Photo analysis by deep neural network algorithm	No	No	Real-time	70.2%[72]	72.7%[72]	?

Table VIII: Summary of Oral Pharmacological Treatment Options for Onychomycosis

	MECHANISM OF ACTION	TYPE OF ACTION	EFFECTIVE AGAINST	INDICATION	CONTRAINDICATION	TYPICAL TREATMENT REGIMEN			DURATION OF ACTION AFTER DISCONTINUATION	CURE RATE (%)			MOST COMMON SIDE EFFECTS	COMMON PHARMACOLOGICAL INTERACTIONS
						DOSE	DURATION			MYCOTIC	CLINICAL	COMPLETE		
							Fingernails	Toenails						
TERBINAFINE	Inhibition of fungal squalene epoxidase	Fungicidal	- Dermatophyte - NDMs - Some yeasts	- First line treatment for dermatophyte onychomycosis - Generally preferred over itraconazole	- Hepatic impairment - Renal Impairment	250mg per day	6 weeks	12 weeks	15-20 days	76%[89]	66%[89]	44-46%	- Gastrointestinal disturbances - Headache - Altered taste perception - Dermatitis	**Drugs metabolized by CYP2D6:** - Tricyclic antidepressants - Serotonin Specific Reuptake Inhibitors - Beta-blockers - Class 1C antiarrhythmics - Type B MAO inhibitors
ITRACONAZOLE	Inhibits fungal cytochrome P450	Fungistatic	- Dermatophyte - *Aspergillus spp.* - *Candida spp.*	- If negative reaction to terbinafine - Agent identified as NDMs or yeasts	- Severe heart failure	**CONTINUOUS:** 200mg per day	6 weeks	12 weeks	6-9 months	**CONTINUOUS:** 69%	70%[89]	21-22%	- Gastrointestinal disturbances - Headache - Upper respiratory infection - Hipertrigliceridemia - Hepatic dysfunction	- Benzodiazepines - Calcium channel blockers - Proton pump inhibitors - Statins - Warfarin - Z drugs
						PULSE: 200mg 2x per day for one week per month	8 weeks (2 pulses)	12 weeks (3 pulses)		**PULSE:** 63%				
FLUCONAZOLE	Inhibits fungal cytochrome P450	Fungistatic	- Dermatophyte - *Candida spp.*	- Onychomycosis by Candida - If negative reaction to terbinafine and itraconazole	- Hepatic impairment - Renal Impairment	150mg once per week	12 weeks	>24 weeks	5 months	61.6%[105]	46.7%	-	- Gastrointestinal disturbances - Headache - Skin rashes - Insomnia	- Benzodiazepines - Calcium channel Blockers - Statins

Legend: MAO – monaminase oxidase inhibitors

Table IX: Summary of Topical Pharmacological Treatment Options for Onychomycosis

	CLASS OF DRUG	TYPE OF ACTION	MECHANISM OF ACTION	EFFECTIVE AGAINST:			POSOLOGY	RECOMMENDED USE	MYCOLOGICAL CURE RATE
				Dermatophytes	NDMs	Yeasts			
AMOROLFINE 5%	Morpholine	Fungistatic and fungicidal	Inhibits ergosterol synthesis and causes accumulation of precursor sterols	✓	✓	✓	1 x per week for 24 - 48 weeks **Fingernails:** 24 - 36 weeks **Toenails:** 36 - 48 weeks	Mild cases of SWO or DLSO Without matrix involvement, in up to 2 nails	70.6%[119]
CICLOPIROX 8%	Hydroxypyridone	Fungicidal	Chelates metal cations which inhibits vital fungal enzymes	✓	✓	✓	1 x daily for up to 48 weeks **Fingernails:** 24 weeks **Toenails:** 36 – 48 weeks	Mild to moderate SWO or DLSO without lunula involvement, particularly due to *T. rubrum* or *Candida spp.*	29%–36%[214]
TAVABOROLE 5%	Oxaborole	Fungistatic	Protein synthesis inhibitor	✓*	-	-	1 x daily for up to 48 weeks**	Toenail onychomycosis by **T. rubrum* or **T. interdigitale*	30%–36% [215,216]
EFINACONAZOLE 10%	Triazole	Fungistatic	Inhibits ergosterol synthesis	✓	✓	✓	1x daily for up to 48 weeks**	Mild to moderate cases of DLSO	53%–56%[129,130]

Legend: * By *T. rubrum* or *T. interdigitale*

** No recommendations are available for treatment of fingernails

Table X: Summary Nail Plate Debridement Options

NAIL PLATE DEBRIDEMENT	
CHEMICAL	PHYSICAL
- Urea (>10%) - Salicylic Acid (>5%) - Thioglycolic acid - Dimethylsulfoxide - Fungal hydrophobins - Acid Etching *- 10% phosphoric acid* *- 20% tartaric acid*	- Mechanical abrasion using files - Microporation - Complete or partial surgical avulsion

Table XI: Summary of Device Based Therapies for Use in Onychomycosis

	LIGHT SOURCE OR WAVELENGTH INVOLVED	MECHANISM OF ACTION	DOMICILIARY OR IN-OFFICE	TYPICAL NUMBER OF SESSIONS	INTERVAL BETWEEN	MECHANICAL EFFECT	THERAPEUTIC EFFECT	PENETRATION ENHANCEMENT EFFECT	SIDE EFFECTS
PHOTODYNAMIC THERAPY	Light source (LED lamp, red-light) Photosensitiser Agents: - Methylene blue dye - Toluidine blue - Porphyrins - Phthalocyanine - 5-Aminolevulinic acid - Methyl-aminolevulinate	Photosensitiser agents absorb energy and generate reactive oxygen species within the fungal cells.	In - office	3 – 12	1 -2 weeks	✓	✓	×	Transient pain and burning sensation
Nd:YAG	1064 - 1444nm	Photothermal effect creates localized increase in temperature destroys and inhibits the growth of fungal cells.	In- office	1-12	1 -4 weeks	✓	✓	✓	Transient pain and burning sensation
FRACTIONAL CO_2	10600nm	Photoablation: Localized increase in temperature decomposes the infected tissue with a sterilizing effect	In - office	1 -12	1 -2 week	✓	✓	✓	Transient pain and burning sensation
ULTRAVIOLET - C	200-280nm	Sterilization of surfaces and reservoirs	Domiciliary	-	-	×	×	×	-
ULTRASOUND	20Hz – 1MHz	Cavitation effects and frequency waves enhance transungual permeation	In-office or domiciliary	-	-	×	×	✓	-
IONTOPHORESIS	Mild electrical field	Increases molecular transport of active drugs using a mild electrical field	In-office or domiciliary	-	-	×	×	✓	-

Table XII: Summary of Cure Criteria in Onychomycosis

COMPLETE CURE	
MYCOLOGICAL CURE	CLINICAL CURE
Negative microscopy and culture	80-100% clinically healthy nail plate

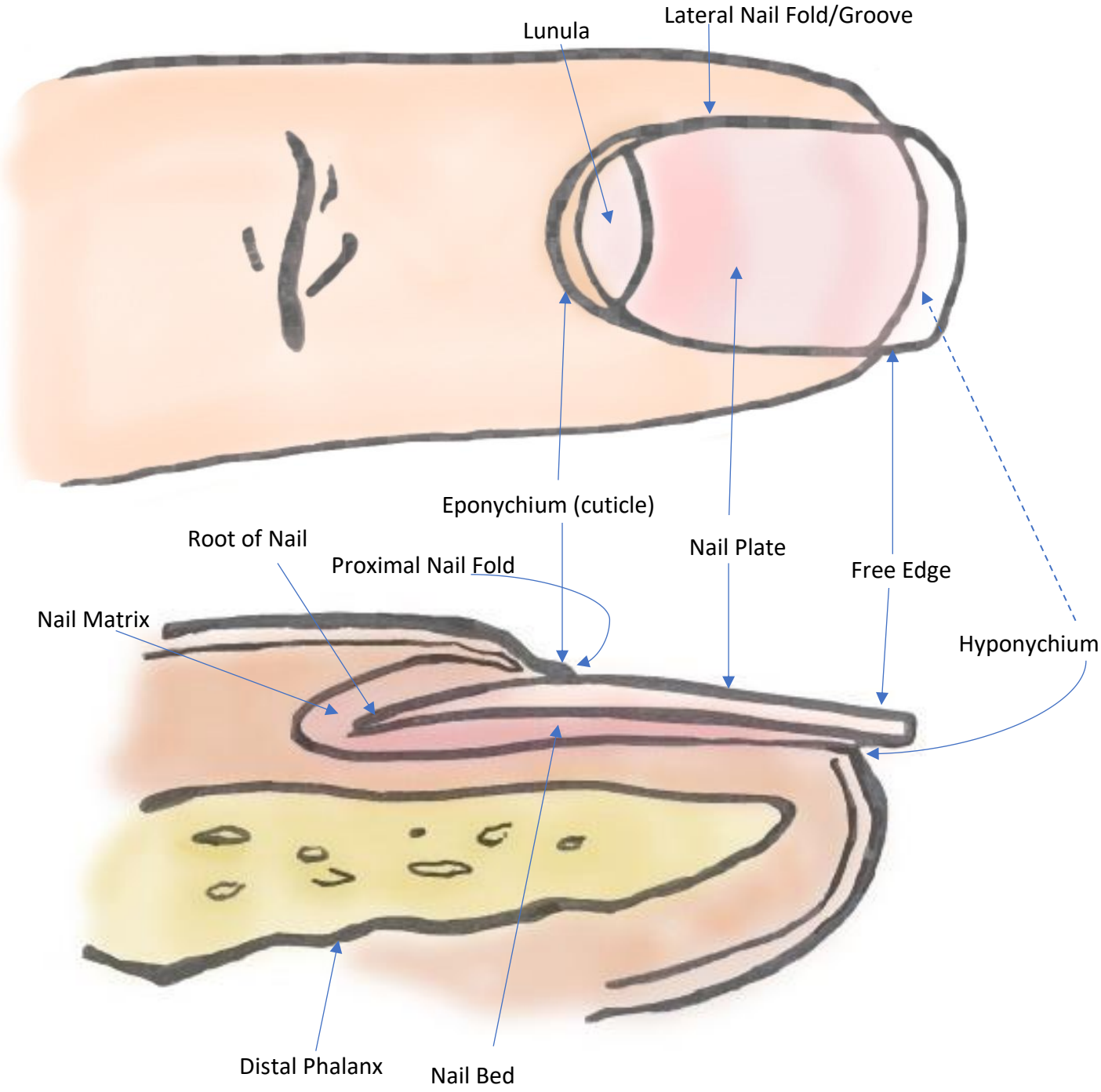

Fig. 1 Anatomical Structure of the Nail Unit

Top figure - dorsal view of nail unit, Bottom figure - sagittal view of the fingertip.
Drawing by the author.

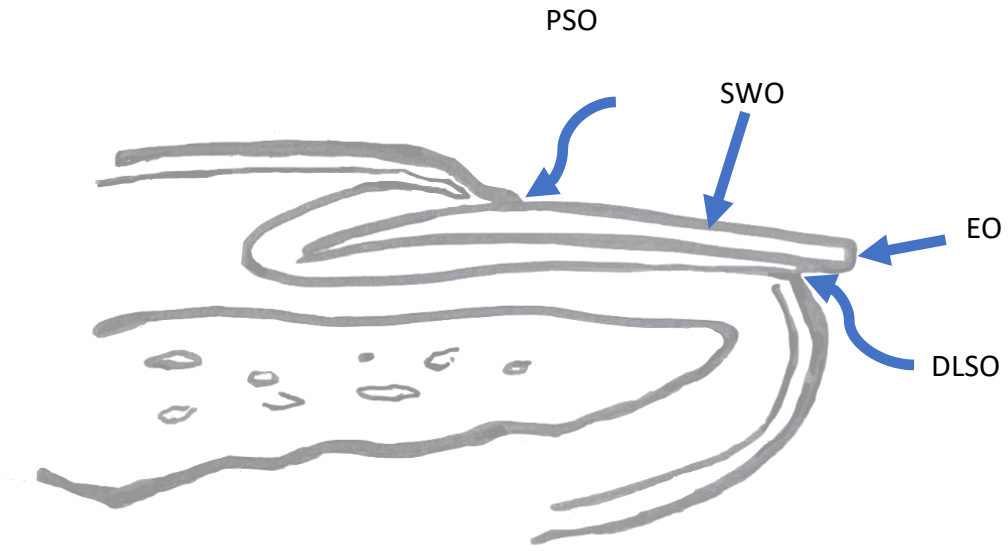

Fig. 2 Nail Unit and Sites of Invasion in Onychomycosis

PSO – Proximal Subungual Onychomycosis invading from the eponychium/proximal nail edge.
SWO – Superficial White Onychomycosis invading via the surface of the nail plate.
EO - Endonyx Onychomycosis with fungal invasion directly through the nail plate in the absence of , subungual hyperkeratosis or onycholysis.
DLSO – Distal Lateral Subungual Onychomycosis invading from the hyponychium or via the lateral nail folds.
Drawing by the author.

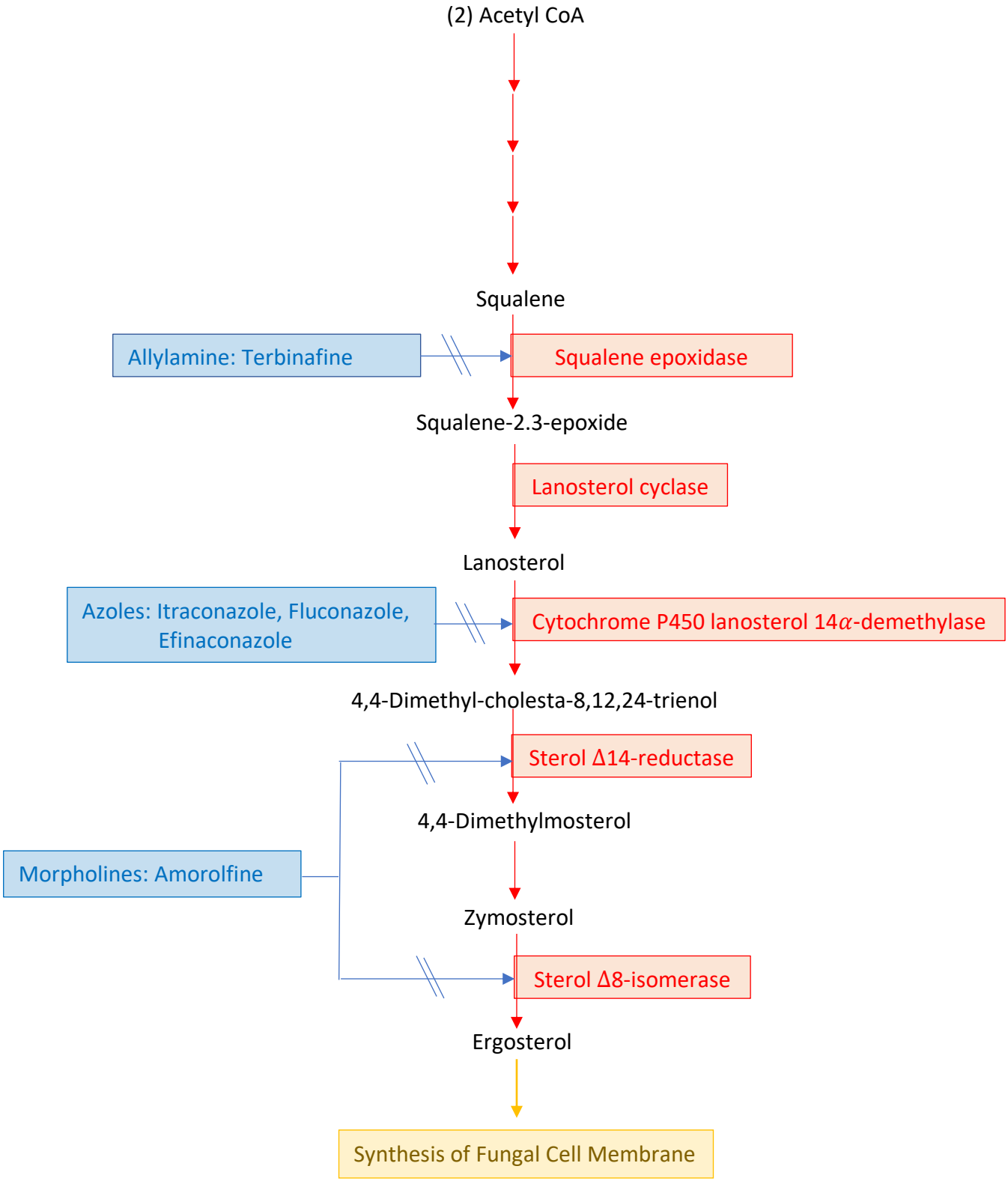

Fig. 3 Ergosterol Synthesis and Target Location of Different Antifungals

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