https://doi.org/10.48047/AFJBS.6.2.2024.4502-4512

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

An Overview about Management Lines of Onychomycosis

Aya Lotfy Mohammed Abdallah

Dermatology, Venereology and Andrology, Faculty of medicine, Zagazig university, Egypt

Corresponding author: Aya Lotfy Mohammed Abdallah

Email: drayalotfy@gmail.com

Article History

Volume 6, Issue 2, Apr-Aug 2024

Received: 5 July 2024

Accepted: 20 July 2024

Published: 25 July 2024

doi:10.48047/AFJBS.6.2.2024.4502-4512

Abstract: Background: Background: Onychomycosis is a mycotic nail infection caused by dermatophytes, yeasts or non-dermatophyte molds (NDM) and account for 30% of all mycotic cutaneous infections and roughly 50% of all nail disease. Confirmatory testing should be performed before initiating treatment for onychomycosis.Direct microscopy, fungal culture, and histopathology may be used for confirmation.Polymerase chain reaction may be used to rapidly identify the infecting organism. Onychomycosis is caused by dermatophytes, nondermatophyte molds (NDM), and yeasts. More than 60% to 70% of these infections are caused by dermatophytes, predominantly Trichophyton rubrum (50%) and Trichophyton mentagrophytes (about 20%), with remaining infections caused by Epidermophyton floccosum, Microsporum spp., Trichophyton violaceum, Trichophyton verrucosum, Trichophyton krajdenii, and Arthroderma spp. Based on their targets for antifungal therapy , antifungal agents can be classified in the following groups: Inhibitors of ergosterol biosynthesis: Ergosterol is the major component of the fungal cell membrane .It is responsible for many cellular actions such as fluidity and integrity of the membrane and the proper function of membrane-bound enzymes. Fungal membrane disruptors: Polyenes were the first antifungal drugs for clinical use.They are fungicidal and have the broadest spectrum of activity compared to any other antifungal molecules. Nystatin, natamycin and amphotericin B are the only three polyenes in clinical use. Fungal cell wall synthesis: Inhibitors b-glucan synthesis: Glucans are polysaccharides that consist of D-glucose monomers attached to each other by b-(1,3) or b-(1,6)-glucan linkages. B-(1,3)-D-Glucan constitutes more than 50% of the fungal cell wall and is the main structural polysaccharide to which other cell wall components (chitins and glycoproteins) are attached. Chitin synthesis inhibitors: Chitin is a minor component of the cell wall ,The synthesis of chitin is mediated by several enzymes named chitin synthases

Keywords: *Onychomycosis, Management Lines*

Introduction Onychomycosis is a mycotic nail infection caused by dermatophytes, yeasts or non-dermatophyte molds (NDM) and account for 30% of all mycotic cutaneous infections and roughly 50% of all nail disease (**1)**.

Toenail involvement is approximately ten times more common than fingernail involvement (**2).**

Onychomycosis is difficult to treat with common relapses and reinfection.The overall incidence of onychomycosis is approximately 5.5% worldwide**.** Previous estimates worldwide were 0.44% to 2.6% in children and prevalence increases with age(**3).**

Clinical picture

History

Patients with onychomycosis often complain of nail discoloration, nail separation, brittleness, or thickening that often worsens with time a history of tinea pedis or hyperhidrosis of the feet is common (**4)**.

Nails affected by onychomycosis may cause local pain, difficulty in fitting shoes, social embarrassment, and have a negative impact on the quality of life **(5).**

Physical examination

In evaluating a patient with nail disease, all 20 nails should be examined as well as the hands and feet. Patients are instructed to remove all nail polish before the examination. Typical physical examination findings include hyperkeratosis of the nail bed, with varying degrees of onycholysis **(5).**

A white or yellow discoloration of the nail plate is common as well as subungual debris. In long-standing or severe cases there may be extensive onychodystrophy with nail plate thickening, crumbling, ridging, onychocryptosis, and partial or complete nail loss.Violaceous,brown or black nail plate discoloration may also be present **(5).**

The dermatophyte T. rubrum var. Nigricans instead causes longitudinal melanonychia in which the band is usually wider distally and narrows proximally. Longitudinal melanonychia, because of benign melanocytic activation, may be caused by candida species, particularly in patients with higher fitzpatrick skin types. Scytalidium dimidiatum, aspergillus niger produce diffuse brown to black pigmentation of the nail plate (**6).**

Onychomycosis may be presented by dermatophytoma, or fungal abscess which is a white/yellow or orange/brown longitudinal streak in the nail plate and it is quite specific for onychomycosis **(5).**

Fungal pathogens causing onychomycosis

Onychomycosis is caused by dermatophytes, nondermatophyte molds (NDM), and yeasts. More than 60% to 70% of these infections are caused by dermatophytes, predominantly Trichophyton rubrum (50%) and Trichophyton mentagrophytes (about 20%), with remaining infections caused by Epidermophyton floccosum, Microsporum spp., Trichophyton violaceum, Trichophyton verrucosum, Trichophyton krajdenii, and Arthroderma spp. Non dermatophytes are responsible for approximately 20% of fungal nail infections and the most common organisms are scopulariopsis brevicaulis, aspergillus spp., acremonium, fusarium spp., alternaria alternate, and neoscytalidium .Yeasts, including candida spp., account for 10% to 20% of onychomycosis cases. **(7).**

Dermatophytes

Dermatophytes are a group of filamentous fungi referred to as the ringworm fungi. They are keratinolytic and invade keratinized tissues causing mostly superficial infections involving the skin, hair and nails. They are the most common causes of skin disease in the world, and the real prevalence is probably underestimated. The primary mode of dermatophyte transmission is shedding of infected skin cells and hair. Transmission by direct contact is limited **(8).**

The adherence of dermatophytes is mediated by proteases that are secreted by them. *T. rubrum* has the capability to attach to epithelial cells by carbohydrate-specific adhesins that are expressed on the surface of arthroconidia, which is the infectious agent. Following the adherence of arthroconidia to keratinized tissue, their growth and germination proceed in a radial manner, expanding in multiple directions. **(9).**

Upon establishment, the spores undergo germination and subsequently penetrate the layer of the stratum corneum. This penetration is accompanied by the keratinases found in the dermatophytes. Fungal metabolic products diffuse through the malpighian layer, causing erythema, vesicle building, and pruritus. **(10).**

After the dermatophytes have invaded and contaminated the stratum corneum, the next phase is retention, during which they remain in the stratum corneum and rarely progress deeper into the epidermis than the surface and its extensions (**10).**

Dermatophytes are divided into three closely related genera: Epidermophyton, Trichophyton and Microsporum.The main characteristic of these fungi, with the exception of keratinophily, is their membership

of a group that depends on their normal habitat: geophilic dermatophytes are naturally present in the soil, zoophilic in animals, and anthropophilic in humans **(11)**.

The fungal pathogens that infect humans belong mostly to the second and third groups,geophilic dermatophytes being more rarely involved in human disease. Zoophilic and anthropophilic dermatophytes evolved from a geophilic origin, with the anthropophilic dermatophytes being the most highly specialized group **(11)**.

They rarely infect other animals and they are also restricted to some body parts. Some species including Microsporum audouinii, Trichophyton tonsurans and Trichophyton soudanense mostly cause Tinea Capities and are rarely isolated from other body sites **(11)**.

Risk factors associated with onychomycosis include the following : advanced age, genetic susceptibility, foot deformities, and comorbidities such as diabetes, immunosuppression, venous insufficiency, peripheral arterial diseases, malignancy, and obesity **(5).**

Dermatologic conditions: previous or concurrent tinea pedis, psoriasis, and hyperhidrosis. Exogenous factors: trauma, poor nail grooming, participation in sports activities,occupational exposure, smoking, and wearing occlusive footwear **(5).**

Non dermatophytes

Non-dermatophyte onychomycosis (NDO) is caused by hyaline and dematiaceous filamentous fungi that are commonly found as soil saprophytes or plant pathogens. Unlike dermatophytes, they are generally not keratinolytic. They live on the unkeratinized intercellular cement of the host tissue and must take advantage of previous keratin destruction by dermatophytes, trauma, or another nail disease. For this reason, they are sometimes considered secondary invaders of the nail plate (**12**).

The list of NDM species that have occasionally been isolated include *Scopulariopsisbrevicaulis* spp., *Fusarium* spp., *Acremonium* spp., *Aspergillus* spp.,and *Scytalidium* spp.(**12**).

Aspergillus species accounts for 0.5–3% of all cases of onychomycosis. Generally, *Aspergillus niger* and *Aspergillus flavus* are the commonest species group of *Aspergillus* isolated from abnormal nail specimens. *Aspergillus fumigatus*, *Aspergillus terreus* and *Aspergillus nidulans* are also common **(13).**

Aspergillus spp. are widely spread environmental moulds found in soil, decaying vegetation and water and not transmitted from person to person . Infection starts under the nail near the hyponychium or at the lateral nail folds, or on a diseased nail plate colonised by *Aspergillus* spp **(13).**

Onychomycosis due to *Aspergillus* spp. is usually a distal–lateral subungual onychomycosis (DLSO). The toenails are involved 25 times more frequently than fingernails due to increased exposure to soil, water and decaying vegetation where *Aspergillus* moulds thrive (**14).**

Aspergillus species growing in nature often produces colourful pigments; therefore, an *Aspergillus* nail infection may well appear greenish, black, brown or various other shades (**14).**

One of non dermatophytes causing onychomycosis is *Scopulariopsis*, which are saprophytes found in soil worldwide. Scopulariopsis brevicaulis onychomycosis represents 1~10% of the non dermatophytic onychomycosis cases depending on the population, geographic regions. It may not be possible to distinguish the causative agents between *Scopulariopsis brevicaulis* and dermatophytes, which exhibit fragile nails with yellowish brown discoloration. Therefore, KOH examination and culture isolation are necessary for distinction. Thick-walled large conidiophores (4~9 μm) with chains of rough-walled, lemon-shaped conidia may be confirmed for the presumptive identification **(15).**

Alternaria spp. rarely causes disease in normal individuals despite its widespread distribution in nature. However, there is an increasing rate of infection caused by spp. in immune-suppressed patients . Onychomycosis due to alternaria species associated with a history of nail trauma or contaminations with soil**.** Specific risk groups have been identified where non-dermatophyte onychomycosis is found. These include

patients with diabetes mellitus , people of older age, patients with peripheral vascular disease , chronic systemic disease and immunosuppression in whom yeast infections occur more frequently **(16).**

A review of 42 epidemiological studies revealed that *Aspergillus* spp. are involved in onychomycosis in < 1% to 35% of cases in the general population and in up to 71% of cases among diabetic and elderly patients.Additionally, psoriasis patients have an increased rate of non-dermatophyte mould infections of their nails with psoriatic pathology **(16).**

The clinical manifestations of dermatophyte and non- dermatophyte mycoses may be largely indistinguishable.However, Non dermatophyte mould infections tend to be more commonly associated with periungual inflammation**(7).**

The criteria for a diagnosis of Non dermatophyte onychomycosis was made based on nail abnormalities consistent with this diagnosis, a positive KOH preparation with the presence of specific hyphae in the nail keratin, and, when the culture was done, the failure to isolate a dermatophyte in the culture and growth of identical mold colonies in the inoculation sites of the culture media. (**17**).

Candida

Candida is part of normal body flora of the oral cavity, gastrointestinal tract and it is also commonly found on the skin**.** It thrives in warm and moist conditions . It exists in oval yeast like forms, up to 5 µm in diameter, and produces pseudohyphae and hyphae. Cutaneous candidiasis is superficial infections of skin, nails, inter digital space and mucus membranes caused by the yeast Candida, especially Candida albicans. Risk factors include antibiotics, corticosteroids, diabetes, elderly, obesity, immunosuppression, animmunodeficiency **(18**).

The groin region, feet, armpits, under the breast in women and the buttock region in babies (diaper dermatitis), corner of the mouth are more common sites.Candida of the skin usually is not contagious. However, people with weak immune system may develop the condition after touching the skin of the infected person. The virulence of Candida albicans arises from the synergistic actions of several aggressive mechanisms such as the high production capacity of host tissue degrading exoenzymes proteinase and phospholipase, morphological dimorphism and phenotypic switching. These mechanisms could alter the adherence to epithelial cells, susceptibility to antifungals, fungicidal activity of neutrophiles and production of toxins ,accompanied by weakness of the host immune response **(19)**

Candidal onychomycosis

Candida species other than *Candida albicans* such as *Candida krusei*, *Candida parapsilosis, Candida glabrata* and *Candida tropicalis* have also been found to cause onychomycosis . Interestingly, a Brazilian study that examined 200 mycological samples from infected nails has shown that the leading pathogen is *Candida parapsilosis* (40.5%) followed by *Candida albicans* (31.5%), *Candida tropicalis* (26%) and *Candida guilliermondii* (2%) (**20)**.

Candida affected nails show severe dystrophic changes of the nail fold and marked thickening, distortion and fragmentation of the nail substance. Pigmentation of nail tissue is a remarkable clinical feature of candidal onychomycosis. Sometimes, candidal onychomycosis may appear with paronychia with white yellow discoloration and with a wavy structure of affected nail plates (**21)**.

Strikingly, diffused melanonychia (black nail), which became intense with the paronychial inflammation due to *Candida albicans* has been demonstrated in a fingernail of a white male**.** These investigators noted that the infected nail was fragile with the increasing intensity of the pigmentation. The pigmentation was attributed to melanin produced by *Candida albicans* (**21)**.

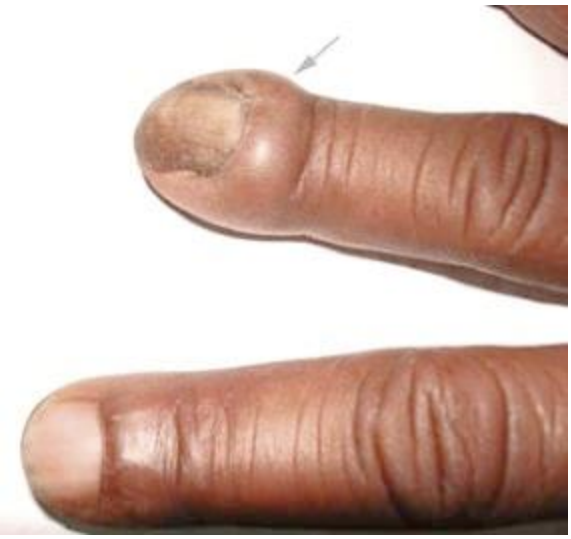

Fig. 1 Candidal paronychia resulting rough, irregular dystro- phic nail. Surrounding soft tissues demonstrate inflammation with swelling (*arrow*) (**20)**.

Candidal onychomycosis is common in women. Thus, it has been postulated that women self- inoculate their nails from their vaginal candidal flora . Yet another possible cause for is that they frequently handle water, detergents and soap during household work, and their fingernails are prone to trauma in case of housewives (**20)**.

Usually, routine diagnostics are done using direct microscopy with 10% KOH. More effective mycological cultures are done using Sabouraud dextrose agar. Positive microbiological cultures would provide characteristic cream to white color colony growth on Sabouraud dextrose agar. As part of the diagnosis, antifungal susceptibility test may be useful for selection of the most suitable drug for treatment (**20)**.

Interestingly, the simplest direct microscopy has yielded better results when compared with culture techniques in the diagnosis of onychomycosis**.** Microscopic investigations into nail clippings show characteristic hyphal invasion of nail substance particularly via hyponychial epithelium . Such invasion can be clearly demonstrated using Periodic acid Schiff (PAS) or Grocott's methanamine silver stains (**22)**.

Antifungal agents and resistance

Classification of Antifungal Agents

Based on their targets for antifungal therapy , antifungal agents can be classified in the following groups:

1-Inhibitors of ergosterol biosynthesis:

Ergosterol is the major component of the fungal cell membrane .It is responsible for many cellular actions such as fluidity and integrity of the membrane and the proper function of membrane-bound enzymes. **(23).**

A .Azoles

Azoles are the most common antifungal drugs clinically used. They are commonly used in the treatment and the prevention of mycoses due to their broad spectrum activity. Azoles inhibit the cytochrome P450-dependent enzyme 14 alpa-lanosterol demethylase (CYP51) encoded by the ERG11 gene that converts lanosterol to ergosterol in the cell membrane inhibiting fungal growth and replication **(23).**

This enzyme contains an iron protoporphyrin unit at its active site. Azoles bind to the iron of the porphyrin and blocks the fungal ergosterol biosynthesis pathway resulting in the accumulation of 14-methylated sterols .The active site of P450 mono-oxygenases differs between fungal species and among the many mammalians. The nature of the interaction between each azole molecule and each kind of P450 determines their antifungal characteristics and side effects. **(23).**

The azoles are cyclic organic molecules that can be classified into two groups: imidazoles and triazoles. Imidazoles (clotrimazole, miconazole and ketoconazole) were the first developed azoles They have high

toxicity,severe side effects and numerous interactions with other drugs so they were replaced by the triazoles**(20).**

The first generation triazoles(Itraconazole and Fluconazole) have a broader antifungal activity spectrum as compared to the imidazoles and proved to be more safe. Fluconazole is active against Candida species, Cryptococcus neoformans, Histoplasma, Blastomyces and Coccidioides species, but lacks activity against molds **(24).**

Itraconazole shows a broader spectrum of activity against yeasts and Aspergillus species**.** However, both have certain clinical limitations as they are ineffective against some emerging pathogens as Scedosporium, Fusarium and Mucorales**.** Azole resistance is increasing mainly due to its fungistatic nature instead of fungicidal nature **(20).**

Second generation of triazoles include Voriconazole and Posaconazole, were approved by the US Food and Drug Administration (FDA) in 2002 and 2006, respectively**.** They are considered fungicidal and have a broad spectrum of activity including Fusarium, Scedosporium, Zygomycetes and Cryptococcus neoformans (**25)**.

Voriconazole became the first-line antifungal drug for the treatment of invasive aspergillosis due to A. fumigatus since its activity is superior to many other antifungals **(*26*).**

Posaconazole has the broadest activity among azoles group and was approved by FDA for prophylaxis against invasive Aspergillus and Candida infections **(23).**

Efinaconazole is a topical antifungal solution active against dermatophytes and nondermatophytes, effective in treatment of onychomycosis, as well as Candida spp. It was approved by FDA in 2014 for the treatment of fungal nail infections (**25)**.

Isavuconazole is the most recently approved triazole for the oral and intravenous treatment of invasive aspergillosis and mucormycosis (**25)**. It has some advantages compared with other approved azoles as it has expanded activity that includes Zygomycetes such as Rhizopus, Mucor and Cunninghamella species. Additionally, its intravenous preparation lacks cyclodextrin that is associated with nephrotoxicity in patients. **(27).**

B. Allylamines

They are synthetic fungicidal agents that block ergosterol biosynthesis as they are reversible, non-competitive inhibitors of squalene epoxidase (ERG1). This enzyme catalyzes the conversion of squalene into 2,3-squalene epoxide. The inhibition of this enzymatic activity leads to squalene accumulation that may increase permeability leading to disruption of cellular organization. Important members of this group include terbinafine and naftifine**.** Terbinafine was isolated from cultures of Streptomyces sp. KH-F12. It is active against Aspergillus, Fusarium and other filamentous fungi **(23).**

It is widely used for the treatment of nail infections. Naftifine is active against Trichophyton, Epidermophyton and Microsporum with Fungistatic activity against Candida species **(28).**

C. Morpholines

The amorolfine is a synthetic water soluble morpholine derivative that inhibits two enzymes involved in ergosterol biosynthesis, D7–D8 isomerase (ERG2) and the D14-reductaseERG24) .Amorolfine is used in the topical treatment of nail infections and it has both fungistatic and fungicidal activity in vitro **(29).**

2. Fungal membrane disruptors

Polyenes were the first antifungal drugs for clinical use.They are fungicidal and have the broadest spectrum of activity compared to any other antifungal molecules. Nystatin, natamycin and amphotericin B are the only three polyenes in clinical use **(29).**

Nystatin and natamycin are active against Cryptococcus, Candida, Aspergillus and Fusarium.Nystatin is used for the treatment of cutaneous, vaginal and esophageal candidiasis,and natamycin can be used for the treatment of fungal keratosis or corneal infections**.** Nystatin and natamycin are only used as topical agents due to their low absorption in the gut and their high toxicity **(23).**

Amphotericin B is active against most yeasts and filamentous fungi. It is recommended for the treatment of systemic infections caused by Candida, Aspergillus, Fusarium, Mucor, Scedosporium and Cryptococcus among others **(29).**

Due to its hydrophobicity and poor absorption through the gastrointestinal tract, it is administered intravenously which causes adverse effects in kidneys and liver.Due to their amphiphilic structure, polyenes can bind to the lipid bilayer and form a complex with the ergosterol producing pores. Pore formation promotes disruption of the cell membrane, the leakage of the cytoplasmic contents and oxidative damage result in fungal cell death **(23).**

3.Fungal cell wall synthesis

A. Inhibitors b-glucan synthesis

Glucans are polysaccharides that consist of D-glucose monomers attached to each other by b-(1,3) or b-(1,6)-glucan linkages. B-(1,3)-D-Glucan constitutes more than 50% of the fungal cell wall and is the main structural polysaccharide to which other cell wall components (chitins and glycoproteins) are attached. **(30)**

The available antifungal drugs targeting cell wall are three echinocandins (caspofungin, micafungin and anidulafungin). They have fungicidal activity against most candida strains and fungistatic against aspergillus **(31).**

Echinocandins act as noncompetitive inhibitors of b-(1,3)-D-glucan synthase enzyme complex which leads to disruption of the structure of growing cell walls, resulting in osmotic instability and fungal cells death **(23).**

Echinocandins show very good safety profiles and their toxicity is very low due to their unique target, that is absent in mammalian cells and interactions with other drugs are minimal. These drugs are poorly absorbed in the gastrointestinal tract because of their high molecular weights. They have a short half-life so they must be administered once-daily intravenously limiting their use to the hospital. Efforts to obtain new echinocandins are relevant since these compounds show broad spectrum antifungal activity and a possible use in combination with azoles or amphotericin B could enhance their action against fungal pathogens without causing the development of resistant strains **(32).**

B. Chitin synthesis inhibitors

Chitin is a minor component of the cell wall ,The synthesis of chitin is mediated by several enzymes named chitin synthases.

Chitin provides structural integrity and when its synthesis is disrupted, the cell wall becomes osmotically unstable.Because chitin is absent in human cells, it is considered an excellent target for antifungal agents. The most widely studied chitin synthase inhibitors are Nikkomycins and Polyoxins,the latter is no longer in development. Nikkomycin is active against highly chitinous dimorphic fungal pathogens and it is not active against neither Candida albicans nor C. tropicalis. **(23).**

4. Sphingolipids biosynthesis

Sphingolipids are abundant components of eukaryotic cell membranes and, besides playing a variety of roles in fungal cells, some of them play an important role in fungal pathogenesis **(33).**

Studies have demonstrated that inhibiting the inositol phosphorylceramide (IPC) synthase that transfers the phosphoinositol group from phosphatidylinositol (PI) to the 1-hydroxy group of phytoceramide to form IPC which is a key step in fungal sphingolipid biosynthesis will attenuate the virulence of fungal pathogens. **(23).**

IPC synthase is not present in mammalian cells, so IPC synthase inhibitors could be good candidates to develop antifungal agents **(33).**

5. Nucleic acid synthesis inhibitors

Flucytosine (5-FC; 5-fluorocytosine) is a fluorinated pyrimidine analog with fungistatic activity that interferes with pyrimidine metabolism, as well as RNA/DNA and protein synthesis **(23).**

It is taken up by fungal cells via cytosine permease and converted by cytosine deaminase to 5-fluorouracil (5-FU) which is transformed by UMP pyrophosphorylase into 5-fluorouridine monophosphate (5-FUMP), which

is phosphorylated and incorporated into RNA, instead of UTP, resulting in inhibition of protein synthesis. 5-FU also undergoes conversion into 5-FdUMP (5-fluorodeoxyuridine monophosphate), a potent inhibitor of thymidylate synthase, that inhibits fungal DNA synthesis and nuclear division. This compound is selectively toxic to fungi as there is little or no cytosine deaminase activity in mammalian cells **(34).**

6. Protein biosynthesis inhibitors

Tavaborole is an oxaborole antifungal approved by the FDA in 2014 for the topical treatment of toenail onychomycosis caused by Trichophyton rubrum and T. mentagrophytes.It shows antifungal activities against yeast, molds and dermatophytes **(7).**

Tavaborole inhibits the leucyl-tRNA synthetase, an essential fungal enzyme for protein synthesis.Tavaborole targets this enzyme by binding to the editing site together with tRNA so this cannot complete the amino acid transfer to the ribosome for assembly and protein synthesis is effectively blocked **(35).**

7-Microtubules biosynthesis inhibitors

Microtubules are polymers of alpha and beta tubulin dimers that form a highly organized cellular skeleton in all eukaryotic cells.Antifungal agents like griseofulvin or vinblastine belong to this group. Griseofulvin is a natural product isolated from Penicillium griseofulvin in 1939 and was the earliest inhibitory agent to fungal species . It is toxic to the liver and the spectrum of action is restricted to the dermatophyte fungi.It binds to tubulin, interfering with fungal microtubule assembly and inhibiting mitosis **(23).**

Resistance to Antifungals

In general, clinical resistance is considered to be the persistence or progression of an infection despite appropriate antimicrobial despite appropriate antimicrobial therapy **(36).**

Fungal resistance can be:

i. Microbiological resistance or *in vitro* resistance
ii. Clinical resistance or *in vivo* resistance **(36).**

Microbiological resistance refers to nonsusceptibility of a fungus to an antifungal agent by in vitro susceptibility testing, in which the minimum inhibitory concentration (MIC) of the drug exceeds the susceptibility breakpoint for that organism**.** Microbiological resistance can be primary (intrinsic), where the fungi are resistant to a drug before exposure or secondary (acquired), which develops in response to exposure to an antimicrobial agent.Certain fungal species are intrinsically resistant such as Candida krusei to fluconazole and Cryptococcus neoformans to echinocandins and nonalbicans Candida to 5-flucytosine (5FC**). (36).**

Secondary resistance develops among previously susceptible strains after exposure to the antifungal agent and is usually dependent on altered gene expression, for example, terbinafine resistance in T. rubrum, fluconazole resistance among C. albicans**. (36).**

Clinical resistance is defined as the failure to eradicate a fungal infection despite the administration of an antifungal agent with in vitro activity against the organism. Although clinical resistance cannot always be predicted, it highlights the importance of individualizing treatment strategies on the basis of the clinical situation**. (37)**

1-Fungal Factors responsible for fungal resistance

a-Decreased accumulation of drug within fungal cell: Reducing the accumulation of the drug within the fungal cell is done by increasing the drug efflux mechanism. Multidrug efflux transporters are membrane proteins found in all living organisms. These proteins bind to a variety of structurally and chemically dissimilar compounds and actively extrude them from the cells. Mutations (upregulation or overexpression) of the genes encoding these efflux pumps result in decreased accumulation of the drug in the cell **(38).**

Decreasing the affinity of the drug for its target :

A mutation or overexpression of the gene coding for target enzymes is another mechanism developed by fungi.Mutation in the squalene epoxide (SE) gene (ERG1) leads to an amino acid substitution in the SE making the fungi about 1000-fold less susceptible to terbinafine. **(36).**

Paradoxical effect:

Few yeasts and filamentous fungi are able to grow in elevated echinocandin concentrations much higher than the MICs. This phenomenon is called paradoxical effect or eagle effect,it is strain dependent phenomenon. It is due to the upregulation of the chitin synthesis in the fungal cell wall after drug administration **(37)**

Plasma membrane composition variation

A decrease or total absence of ergosterol in the plasma membrane through mutations in nonessential genes of the ergosterol is a rare mechanism of resistance among polyene drugs, for example, ERG3 mutation in clinical isolates of C. albicans, ERG6 mutation in C. glabrata. **(39)**

Biofilms

Biofilms are sessile microbial communities surrounded by extracellular polymeric substances with increased resistance to antimicrobial agents and host defenses. Both T. rubrum and T. mentagrophytes are capable of producing biofilms. **(40).**

Cellular response to stress or stress adaptation

Fungi are remarkably adaptive and have numerous signal-transduction pathways to sense and ensure appropriate physiological mechanisms to adapt to environmental stress following exposure to an antifungal agent **(36).**

Stress adaptation may not induce clinical resistance but stabilizes the cell in the presence of drug and allows it to develop more profound resistance mechanisms over time that are manifested as clinical resistance. **(38).**

B-Clinical Resistance

Clinical resistance depends on a multiple host- and drug-related factors which are as follows:

1. Patients with severe degree of immunosuppression with invasive fungal infections may not respond to antifungals.
2. Delay in initiation of adequate dose of antifungal results in increased chances of treatment failure.
3. Fluconazole has better cerebrospinal fluid (CSF) penetration as compared to itraconazole, therefore, making it a better choice in treating fungal meningitis. When the site of infection is necrotic with poor blood supply, a debulking surgery is essential to overcome antifungal treatment resistance.
4. Compliance in patients requiring long-term therapies.

(37)

Various drug related factors such as the fungistatic nature of most drugs, inappropriate antifungal usage (in cases where the etiological agent is known), treatment with low antifungal dosage, long duration of treatment, drug interactions, and the cost of therapy play a role in fungal resistance. **(38).** Drug to drug interaction may be the cause of antifungal resistance like Combination of polyenes and azoles with other nephrotoxic drugs can result in treatment failure **(37)**

Environmental resistance

The role of environment as a cause of resistance has become prominent. Fungicidal use in agriculture differs hugely between different regions, with the United States using about a tenth of as much as Europe. Azole-based fungicides are used in grape and cereal production in European countries. A strong link has been found between countries where azole-based fungicides are used and the incidence of antifungal resistance **(38).**.

References

1. Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. J Am Acad Dermatol. 2011;65(6):1219–27.

2. Sigurgeirsson B, Baran R. The prevalence of onychomycosis in the global population: a literature study. J Eur Acad Dermatol Venereol. 2014;28(11):1480–91.
3. Papini M, Piraccini BM, Difonzo E, Brunoro A. Epidemiology of onychomycosis in Italy: prevalence data and risk factor identification. Mycoses. 2015;58:659-664.
4. Augustin M, Radtke MA, Herberger K, Kornek T, Heigel H, Schaefer I. Prevalence and disease burden of hyperhidrosis in the adult population. Dermatology. 2013;227:10-13.
5. Lipner SR, Scher RK. Onychomycosis: Diagnosis and Therapy.In: Razzaghi-Abyaneh M, Shams-Ghahfarokhi M, Rai M, eds. Medical Mycology: Current Trends and Future Prospects. Boca Raton, FL: CRC Press; 2015.
6. Finch J, Arenas R, Baran R. Fungal melanonychia. J Am Acad Dermatol. 2012;66:830-841.
7. A.K. Gupta, S.G. Versteeg, Tavaborole – a treatment for onychomycosis of the toenails, Expert Rev. Clin. Pharmacol. 9 (2016) 1145–1152.
8. White TC, Marr KA, Bowden RA. Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. Clin Microbiol Rev. 1998;11:382–402.
9. Vermout, S.; Tabart, J.; Baldo, A.; Mathy, A.; Losson, B.; Mignon, B. Pathogenesis of Dermatophytosis. Mycopathologia 2008, 166, 267–275.
10. Tainwala, R.; Sharma, Y. K. Pathogenesis of Dermatophytoses. Indian J. Dermatol. 2011, 56, 259.
11. Hayette, Marie-Pierre, and Rosalie Sacheli. "Dermatophytosis, trends in epidemiology and diagnostic approach." Current Fungal Infection Reports 9 (2015): 164-179.
12. Farwa U, Abbasi SA, Mirza IA, Amjad A, Ikram A, Malik N, et al. Non-dermatophyte moulds as pathogens of onychomycosis. J Coll Physicians Surg Pak. 2011;21(10):597–600.
13. Negroni R. Onychomycosis due to Aspergillus species. In: prevention. Dordrecht: Springer Netherlands; 2009. p. 961–71.
14. Banu A, Anand M, Eswari L. A rare case of onychomycosis in all 10 fingers of an immunocompetent patient. Indian Dermatol Online J. 2013;4:302–4.
15. de Hoog, G.S.; Dukik, K.; Monod, M.; Packeu, A.; Stubbe, D.; Hendrickx, M.; Kupsch, C.; Stielow, J.B.; Freeke, J.; Göker, M.; et al. Toward a novel multilocus phylogenetic taxonomy for the dermatophytes. Mycopathologia 2017, 182, 5–31.
16. Reinel D. Non-dermatophyte fungi in onychomycosis-Epidemiology and consequences for clinical practice. Mycoses. 2021 Jul;64(7):694-700.
17. Weisenberg SA, Schuetz AN, Alexander EL, Eiss B, Behta M, Saiman L, et al. Endemic Acinetobacter baumannii in a New York hospital. PLoS One. 2011;6(12):28566.
18. Robinson J. Fungal skin infections in children. Nurs Stand. 2012;27:52- 54,56,58.
19. Sardi JCO, Duquet C, Hofling JF, Gonçalves RB. Genetic a phenotypic evaluation of Candida albicans strains isolated from subgingival biofilm of diabetic patients with chronic periodontitis. Med Mycol 2012; 50: 467
20. Jayatilake JA, Tilakaratne WM, Panagoda GJ. Candidal onychomycosis: a mini-review. Mycopathologia. 2009 Oct;168(4):165-73.
21. Lange M, Roszkiewicz J, Szczerkowska-Dobosz A, Jasiel- Walikowska E, Bykowska B. Onychomycosis is no longer a rare finding in children. Mycoses. 2006;49:55–9.
22. Kwon-Chung KJ, Sugui JA. Aspergillus fumigatus—What makes the species a ubiquitous human fungal pathogen? PLoS Pathog 2013;9:1–4.
23. Campoy S, Adrio JL. Antifungals. Biochem Pharmacol. 2017 Jun 1;133:86-96.
24. P.G. Pappas, J.H. Rex, J.D. Sobel, S.G. Filler, W.E. Dismukes, T.J. Walsh, J.E. Edwards, Guidelines for treatment of candidiasis, Clin. Infect. Dis. 38 (2004) 161–189.
25. L.R Peyton, S. Gallagher, M. Hashemzadeh, Triazole antifungals: a review, Drugs Today 51 (2015) 705–718.
26. K.M. Pianalto, J.A. Alspaugh, New horizons in antifungal therapy, J. Fungi 2 (2016) 1–24ز
27. Ellsworth M, Ostrosky-Zeichner L. Isavuconazole: Mechanism of Action, Clinical Efficacy, and Resistance. J Fungi (Basel). 2020 Nov 29;6(4):324.
28. Ghannoum MA, Mukherjee PK, Warshaw EM, Evans S, Korman NJ, Tavakkol A. Molecular analysis of dermatophytes suggests spread of infection among household members.Cutis. 2013;91:237-245.
29. D.G. Sant, S.G. Tupe, C.V. Ramana, M.V. Deshpande, Fungal cell membranepromising drug target for antifungal therapy, J. Appl. Microbiol. (2016),

30. Lorand, B. Kocsis, Recent advances in antifungal agents, Mini Rev. Med. Chem. 7 (2007) 900–911.
31. R.A. Akins, An update on antifungal targets and mechanisms of resistance in Candida albicans, Med. Mycol. 43 (2005) 285–318.
32. M.A. Pfaller, S.A. Messer, P.R. Rhomberg, R.N. Jones, M. Castanheira, Activity of a long-acting echinocandin, CD101, determined using CLSI and EUCAST reference methods, against Candida and Aspergillus spp., including echinocandin- and azole-resistant isolates, J. Antimicrob. Chemother. (2016).
33. R. Rollin-Pinheiro, A. Singh, E. Barreto-Bergter, M. Del Poeta, Sphingolipids as targets for treatment of fungal infections, Future Med. Chem. 8 (2016) 1469– 1484.
34. C. Zhao, T. Huang, W. Chen, Z. Deng, Enhancement of the diversity of polyoxins by a thymine-7-hydroxylase homolog outside the polyoxin biosynthesis gene cluster, Appl. Environ. Microbiol. 76 (2010) 7343–7347.
35. F.L. Rock, W. Mao, A. Yaremchuk, M. Tukalo, et al., An antifungal agentinhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site, Science 316 (2007) 1759–1761 griseo-fulvum Dierckx, Biochem. J. 33 (1939) 240–248.
36. Martinez-Rossi NM, Peres NT, Rossi A. Antifungal resistance mechanisms in dermatophytes. Mycopathologia. 2008;166:369–83.
37. Kanafani ZA, Perfect JR. Antimicrobial resistance: Resistance to antifungal agents: Mechanisms and clinical impact. Clin Infect Dis. 2008;46:120–8.
38. Perlin DS, Shor E, Zhao Y. Update on antifungal drug resistance. Curr Clin Microbiol Rep. 2015;2:84–95.
39. Vandeputte P, Ferrari S, Coste AT. Antifungal resistance and new strategies to control fungal infections. Int J Microbiol 2012. 2012:713687.
40. Costa-Orlandi CB, Sardi JC, Santos CT, Fusco-Almeida AM, Mendes-Giannini MJ. In vitro characterization of Trichophyton rubrum and T. Mentagrophytes biofilms. Biofouling. 2014;30:719.