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Fungal Resistance: Mechanism and Strategies to Overcome

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Superficial dermatophytoses affecting skin, hair and nail, caused by keratinophilic filamentous fungi of genera Trichophyton, Microsporum and Epidermophyton, are among the most common public health problem in hot and humid climate of tropical countries. Among the fungi isolated from skin infections, the anthropophilic dermatophyte T. rubrum is the most frequent amongst clinical cases of tinea pedis, tinea unguium, tinea corporis and tinea cruris while Trichophyton tonsurans is found as the most likely etiologic agent in cases with tinea capitis.

The fungal cell wall is composed of multiple layers where mannoproteins and glucan make up most of the cell wall composition. Mannoproteins are predominantly expressed at the external surface. The plasma membranes of fungi are primarily composed of ergo sterol [1]. Keratinocytes are the most numerous cells in the epidermis, forming a physical barrier to micro-organisms and mediate the immune response through the various soluble factors, such as growth factors, transforming growth factor, tumor necrosis factor, interleukins, and colony stimulating factors [2]. Recent studies have demonstrated that keratinocytes have a different profile of cytokine expression when stimulated by different species of dermatophytes [3].

Both topical and systemic therapies may be used to treat dermatophyte infections. The binding and synthesis of ergosterol are the targets for several antifungal drugs. Topical therapy is generally found effective for uncomplicated tinea corporis of small areas and of short duration. Antifungals are grouped on the basis of their structure and mechanism of action: The azoles (imidazoles and triazoles) interfere with the ergosterol biosynthesis pathway and are directed against lanosterol 14-alpha-demethylase, a cytochrome P-450 enzyme, in the ergosterol pathway. Polyenes (amphotericin B and nystatin) act by increasing the permeability of the plasma membrane. They bind to fungal membrane sterol, resulting in the formation of aqueous pores through which essential cytoplasmic materials leak out and thereby destroying the proton gradient within the membrane. Allylamines (naftifine, terbinafine and the related benzylamine butenafine) and thiocarbamates (tolnaftate and tolciclate) inhibit the conversion of squalene to 2,3-oxidosqualene by the enzyme squalene epoxidase, leading to intracellular accumulation of squalene which is toxic to fungal cells and leads to cell death. Candins inhibit the synthesis of β 1,3-glucan, the major structural polymer of the cell wall. Morpholines, the recently introduced new class of antifungal drug for topical use, inhibit two enzymes in the ergosterol biosynthetic pathway, C-14 sterol reductase (ERG24) and C-8 sterol isomerise (ERG2) resulting into changes in membrane permeability and disruption of fungal metabolic processes.

Systemic therapy is indicated for tinea corporis that includes widespread skin infection, immunosuppression, resistance to topical antifungal therapy, and comorbidities of tinea capitis or tinea unguium or when the infection involves

hair follicles, such as Majocchi granuloma. The preferred treatment is griseofulvin or terbinafine, although some resistance has developed to oral griseofulvin. The mode of action of griseofulvin is not completely clear, but it has been speculated that griseofulvin inhibits microtubule binding within the mitotic spindle in metaphase, causing arrest of fungal cell mitosis and weakening the cell structure. In addition, griseofulvin and terbinafine induce the cytochrome P-450 enzyme system and can increase the metabolism of CYP-450–dependent drugs. Systemic azoles function similar to the topical agents, causing cell membrane destruction.

Early recognition and treatment is essential to reduce morbidity and possibility of transmission. Treatment of dermatophytosis is generally long and costly. Dermatophytoses are often associated with relapses following the interruption of antifungal therapy. Recently, clinical failure has been observed in patients treated with antifungals and drug resistance has become an important problem. Although the prevalence of drug resistance in fungi is below that observed in bacteria, mycologists now believe that selective pressure will, over time, lead to more widespread resistance [4]. The incidence of fungal infections, including resistant infections, has increased during the past few years, and may be due to inadequate or irregular use of drugs or increased incidence of immunodeficiency states [5]. The increased use and over the counter sale of antifungal agents in recent years has also resulted in the development of resistance to these drugs.

The National Committee for Clinical Laboratory Standards (NCCLS) proposed methods and guidelines for antifungal resistance testing of yeasts [6]. There is currently no susceptibility standard for dermatophytes [7]. The NCCLS Subcommittee for Antifungal Susceptibility Testing recently established interpretive breakpoints for testing of fluconazole and itraconazole for Candida infections [8]. In vitro demonstration of resistance does not necessarily equate to in vivo resistance [7, 9]. Other determinants in the selection of resistance include host-related factors, e.g. immunosuppression, the site and severity of infection and drug pharmacokinetics [10]. The main biochemical and molecular mechanisms that contribute to antifungal resistance include reduced uptake of the drug, an active transport out of the cell or modified drug metabolic degradation of the cell, changes in the interaction of the drug to the target site or other enzymes involved in the same enzymatically by point mutations, overexpression of the target molecule, overproduction or mutation of the target enzyme, amplification and gene conversion (recombination), and increased cellular efflux [11]. An alteration in the quantity or quality of 14α-demethylase in the expression of resistance to azole antifungal agents is observed [12, 13].

The resistance of dermatophytes to agent's inhibitors involves the participation of modifiers target enzymes, overexpression of ABC transporters and stress-related proteins [11]. A role of upregulation of the ERG11 gene, which encodes the major target enzyme of the azoles lanosterol 14α--demethylase, has been observed in azole-resistant C. albicans and C. glabrata isolates [14]. A mutation in the gene encoding the enzyme squalene epoxidase target antifungal terbinafine and gave high resistance to this drug against fungi T. rubrum [15]. Recently, it was suggested that C. albicans may possess one or more additional genes encoding ATP-binding cassette MDR-like proteins that are distinct from CDR1, which could participate in the development of azole resistance. Drug efflux, especially ATP-Binding Cassette (ABC) super family of proteins as an important mechanism of resistance to azole antifungals is forthcoming recently [16]. Another emerging source of antifungal resistance is the occurrence of a biofilm, the extracellular matrices produced by microbes themselves which serve to help organisms attach to living or non-viable surfaces [17]. It has been demonstrated that drug efflux pumps play a role in the drug resistance of early bio films [18]. The MAPK Mkc1p seems to be a regulator of azole resistance in mature bio films [19]. Resistance to polyene antibiotics is found rarely, with resistant isolates being confined mostly to the less common species of Candida, such as C. lusitaniae, C. glabrata, and C. guilliermondii. Although clinical failure has been observed in patients treated with terbinafine, allylamine resistance in association with clinical use of terbinafine and naftifine has not been found in human pathogenic fungi.

However, with the increased use of this agent, resistance may be expected, since Vanden Bossche et al. [20] have reported a C. glabrata strain that became resistant to fluconazole and expressed cross-resistance to terbinafine. CDR1 can use terbinafine as a substrate [21].

The primary factor driving the emergence of antifungal resistance appears to be resulting from the increased use and inappropriate prescribing of systemic antifungal agents. Ghannoum and Rice [12] suggested various measures to avoid and suppress the emergence of antifungal resistance. An increased emphasis on rapid diagnosis of fungi and optimizing therapy according to pharmacokinetic and pharmacodynamic properties and thus reducing exposure to low concentrations of systemic agents has been stressed to be focussed upon. The recent approval of a reference method for the antifungal susceptibility testing of yeast is encouraging and provides a means for performing surveillance studies [22]. Use of combinations of antifungal drugs or use of adjunctive immunostimulatory therapy may be more effective in preventing development of resistance.

Recently, a team of researchers using detailed genetic, biochemical, and molecular approaches, identified a mechanism controlling multidrug resistance in fungi [23]. They found that yeast induce multidrug resistance via a molecular switch similar to one that removes drugs and other foreign substances from human cells. When the yeast protein Pdr1p binds to anti-fungal drugs or other chemicals, it switches on molecular pumps that remove the drugs from the cell. Through a protein called PXR that turns on genes involved in detoxifying and removing drugs from cells. A new way to fight drug-resistant fungal infections targeting heat shock protein 90 has also been suggested which link temperature with the signalling cascades that regulate morphogenesis, fungal development and virulence [24]. Photodynamic therapy has been suggested as an alternative treatment for therapy resistant patients, however, the data on this are still limited and in some cases, the aggravation rates are higher than with other methods [25].An alternative non-invasive treatment protocol utilizing combinations of visible and near infrared laser beams in association with blue, red and ultra-violet Light Emitted Diodes (LEDs), without usage of photosensitizers, with minimal side effects, for therapy resistant patients suffering from Tinea Pedis, Pityriasis versicolor, or Mycetoma has been demonstrated [26].

Antifungal drug resistance is becoming a common problem in patients. Several variables stressed to be considered when trying to minimize the risk for development of resistance, including type of drug, dosing during prophylaxis or treatment, the length of treatment, and the immune status of the patient. Although, there is considerable knowledge concerning the biochemical, genetic and clinical aspects of resistance to antifungal agents, expansion of our understanding of the mechanisms by which antifungal resistance emerges and spreads, quicker methods for the determination of resistance, targeting efflux pumps, especially ATP binding cassette transporters and heat shock protein 90, new drug delivery systems, optimizing therapy according to pharmacokinetic and pharmacodynamic characteristics, new classes of antifungal drugs that are active against azole-resistant isolates, and use of combinations of antifungal drugs or use of adjunctive immunostimulatory therapy and other modalities of treatment will clearly be important for future treatment strategies and in preventing development of resistance.

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