

Current Epidemiology of Antifungal Resistance in Filamentous Fungi

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Abstract

Filamentous fungi are a group of pathogens that cause various diseases ranging from superficial lesions to life-threatening invasive infections. Management of these infections relies on the use of several antifungal drugs including the most common used, azoles, echinocandins and polyenes. However, as observed in bacteria, antifungal drug resistance is emerging worldwide and represent a great concern in the control of these diseases. While reports on the resistance of *Candida* and *Aspergillus* to antifungal agents are widely available in the literature, data describing the susceptibility of dermatophytes and the non-dermatophytes molds are starting to appear. This review summarizes the current situation of the antifungal drug resistance in these filamentous fungi.

Keywords: Antifungal; Drug resistance; Dermatophytes; Molds

Introduction

Fungal infections are increasing significantly in recent years. Diseases caused by fungal species vary from superficial infections located in skin and mucosal areas to invasive infections [1]. Skin and nails fungal infections, generally easy to cure are the most common diseases in humans. The invasive infections causing life-threatening diseases especially in immunocompromised patients are responsible for high mortality rates with around one and a half million deaths every year. Among the causes of these diseases, filamentous fungi characterized by a cottony growth on organic substances are one of the most common groups that infect tissues of humans and animals. In one hand, the species belonging to the group dermatophytes cause infections of the keratinized tissues such as hair, skin and nails. In the other hand, the non-dermatophytic molds including *Aspergillus*, *Fusarium*, *Mucorales* are involved in infections able to cause potential fatal invasive disease. Several

antifungal drug classes including the three major ones azoles, echinocandins and polyenes are used for internal and/or external treatment of filamentous fungal infections [2]. However, the emergence of antifungal drug resistance is gaining importance particularly in the treatment of invasive mycoses as reduced drug susceptibility could be associated to clinical failure [3]. Although several papers describing resistance to antifungal drugs among yeasts and *Aspergillus* are available in the literature, data showing resistance of dermatophytes and the other non-dermatophytic molds are starting to appear [4,5]. In this review, we present the most common fungal diseases due to filamentous fungi, the different antifungal drugs used in their management and the worldwide situation of drug resistance.

Presentation of the Most Common Infections Due to Filamentous Fungi

Filamentous fungi are involved in many infections (superficial or invasive) affecting immunocompetent and immunocompromised patients. Among these diseases, dermatophytosis which affects 20%-25% of the world population is considered as the most common fungal infections worldwide [6]. Dermatophytosis are caused by filamentous fungi called dermatophytes that invade and multiply within keratin-rich tissues (skin, nails and hair). They can be caused by three genera: *Trichophyton* affecting the skin, the hair and the snails; *Epidermophyton* responsible of infections on skin and nails; *Microsporum* which affect skin and hair. The infection also called tinea can be classified according to the affected site as tinea pedis (feet), tinea manuum (hand), tinea cruris (inguinal, pubic, perineal and perianal), tinea corporis (glabrous skin), tinea unguium (nails), tinea barbae (beard men), tinea capitis (the scalp) [7]. Recent reports from the World Health Organization (WHO) have estimated the prevalence of tinea capitis (one of the most common dermatophytosis) at 7%–33% in children from low income countries [8]. Symptoms of tinea capitis vary from broken-off hairs to a painful inflammatory mass in the scalp. For the other tinea, the lesions are variable ranging from

smaller papular areas in tinea cruris to chronic, hyperkeratotic mildly inflammatory type in tinea pedum and manuum.

Another fungal infection due to filamentous fungi is aspergillosis considered as the most common invasive fungal infection which involves respiratory tract. They represent over 85% of invasive mould disease. *Aspergillus*, one of the most important fungal pathogens is a filamentous fungus that can be found everywhere from the tropical/sub-tropical areas (winds of Sahara) to the temperate regions (e.g. snow of the Antarctic) [9]. A fungal spore of this saprophytic microorganism is found in decaying vegetation, soil, water, food, air. Inhalation of the airborne asexual spores is the most important mode of infection and conidia inoculated are cleared by the innate immune system in immunocompetent hosts [1]. However, the spores can cause different forms of pulmonary diseases depending on the degree of inoculum, the lung structure and the host immunity. The pathology varies, ranging from non-invasive disease (colonization or aspergilloma), Allergic Bronchopulmonary Aspergillosis (ABPA) to invasive pulmonary aspergillosis [10] which is considered as the most severe disease caused by *Aspergillus*. Dissemination of the disease is possible and can reach the brain and kidneys, causing high mortality rate in immunocompromised patients [11]. The population at risk of developing these infections includes neutropenic patients, individuals with immunosuppressive treatment (e.g. corticosteroids) and patients with Chronic Obstructive Pulmonary Disease (COPD). Other high-risk group is patients with severe pulmonary disorders such as tuberculosis and systemic inflammatory disease sarcoidosis. *Aspergillus fumigatus* followed by *Aspergillus lavus* and *Aspergillus niger* are the commonest species involved in the majority of these invasive infections.

The other molds most involved in infections particularly in invasive diseases are *Fusarium* and *Mucorales*. In one hand, *Fusarium spp.*, part of a group often referred to as hyphomycetes, are filamentous fungi widely distributed in soil and associated with plants. *Fusarium spp.* is frequently reported as etiologic agent of opportunistic infections in humans causing superficial lesions (keratitis, onychomycosis), allergic diseases and disseminated infections. *Fusarium* species are frequently considered in tropical countries as the most common etiology of fungal keratitis. However, their role in the infection of immunocompetent patient particularly in superficial lesions is still debatable. *Fusarium solani* followed by *Fusarium verticillioidis* and *Fusarium oxysporum* are the most common species [12]. In another hand, *Mucorales* are responsible of Mucormycosis (Zygomycosis or Phycomycosis) which are considered as opportunistic infections. The disease has worldwide distribution and affects immunocompromised individuals such as patients with diabetes mellitus, solid organ transplant recipient. Spores of the filamentous fungus named *Mucorales* are able to disseminate in the organism causing infarction of infected tissues and high mortality rate. Lesions are commonly located in the lungs, the sinuses or the skin [13,14]. *Rhizopus* considered as the chief pathogen, *Rhizomucor* and *Absidia* are the common genera causing Mucormycosis. Spores

of the fungus are found in vegetables, soil and manure. Individuals are contaminated by inhalation of the spores.

Management of Filamentous Fungal Infection and Situation of Antifungal Drug Resistance

Dermatophytosis

Several antifungal drugs are used for the treatment of dermatophytosis. Azole compounds, such as itraconazole, bifonazole and ketoconazole act by inhibiting lanosterol 14 alpha-demethylase and by blocking fungal membrane ergosterol biosynthesis in the cell. Griseofulvin a fungistatic, inhibits the growth of dermatophytes by inhibiting the nuclear acid synthesis and the fungal cell mitosis. The other drugs like terbinafine, an allylamine block the squalene epoxidase of the fungus. Amorolfine, a non-azole antifungal agent, inhibit other pathways of D7-D8 steroid isomerase and D14 sterol reductase in fungal cell [15].

Infections caused by dermatophytes may need long-term therapy with antifungal drugs. This situation can expose to the development of antifungal resistance. Indeed, it is observed in some infections like onychomycosis a prolonged therapy with sometimes low drug concentrations and an important proportion of clinical failures [16]. To date, there are few reports describing the acquired resistance of dermatophytes species to the most common antifungal used. This can be explained by the fact that antifungal susceptibility testing is not performed in routine laboratory for dermatophytes. Hence, it is very likely that the resistance appears but is not detectable. Another explanation could be the very high antifungal concentrations obtained at the infected site after topical use, killing effectively the fungus [3]. Alterations in the molecular mechanisms (efflux pump overexpression or enzyme mutation) responsible for drug resistance, restricted by the slow growth of dermatophytes have been also proposed as possible explanation.

Despite these findings, some studies have described the emergence of *in vitro* resistance in dermatophytes species (**Table 1**). The prevalence of drug resistance varies according to geographical areas and to the species tested. In Mexico, a study has demonstrated by using E-Test and according to CLSI the resistance to azolic compounds of 19.4% of dermatophytes clinical isolates including *Trichophyton rubrum*, *Trichophyton mentagrophytes* and *Trichophyton tonsurans* [17]. In Iran, authors have reported 12% of clinical dermatophytes isolates relatively griseofulvin-resistant. They have tested *T. verrucosum*, *Microsporium canis* and *Trichophyton mentagrophytes* [18]. Recently, a study performed in Turkey has reported similar results showing the low level susceptibility of *Trichophyton mentagrophytes* to griseofulvin [19]. Another study has shown 12 cases (19.7%) and 7 cases (11.5%) of resistance to fluconazole and terbinafine respectively [20].

Table 1: Distribution of dermatophytes isolates resistant to antifungal agents.

Country	Species	Resistance rate in %	Drugs tested	Reference
Mexico	<i>Trichophyton rubrum</i>	19.4	Azoles	[17]
	<i>Trichophyton mentagrophytes</i>			
	<i>Trichophyton tonsurans</i>			
Iran	<i>Trichophyton verrucosum</i>	12	Griseofulvin	[18]
	<i>Trichophyton mentagrophytes</i>			
	<i>Microsporum canis</i>			
Turkey	<i>Trichophyton mentagrophytes</i>	-	Griseofulvin	[19]
USA	<i>Trichophyton rubrum</i>	-	Terbinafine	[21]

Another species which show relatively low level susceptibilities against some antifungal drug is *Trichophyton rubrum*. This dermatophyte is known to be a major causative agent of tinea pedis and onychomycosis and is involved in 69.5% of all dermatophytosis. In USA, clinical *T rubrum* isolates have been reported to be resistant *in vitro* to terbinafine a very widely used drug in dermatophytosis, both orally and topically. The six *T rubrum* strains tested in this study were obtained from a patient who failed oral terbinafine treatment [21]. According to the authors, a previous study based on Random Amplified Polymorphic DNA (RAPD) analyses and antifungal susceptibility testing had revealed that the failure of certain patients to clear *T rubrum* was not related to drug resistance but likely to host factors.

Aspergillosis

Triazole antifungals are the recommended drugs for the treatment and the prophylaxis of aspergillosis. Unfortunately, there are many reports describing the emergence of azole resistant *Aspergillus fumigatus* isolates both from clinical setting and the environment [22]. Most of these reports come from Europe, where several studies have shown the spread of azole resistance in this continent (Table 2). A recent prospective multicenter study on the international surveillance on azole resistance in *Aspergillus fumigatus* has reported an overall prevalence at 3.2% (range 0.0%–26.1% among the centers). The acquired azole resistance cases were detected in 11 of 17 European centers in 9 countries [23]. The authors have reported the TR34/L98H as the predominant mechanism of resistance (48.9%) raising the concern that resistance selection in the environment contributes to azole-resistant aspergillosis. The distribution of azole resistance is not uniform within the European continent varying from high prevalence rates reaching sometimes 27.8% in UK to low prevalence rate in Spain (2.5%).

In Asian region, prevalence of azole resistance in *Aspergillus fumigatus* clinical isolates are variables according to the

countries ranging from 1.9% (2/103) in India to 27.5% (8/29) in China [24] (Table 2). Resistance genotypes detected in several *Aspergillus fumigatus* clinical isolates have been confirmed to be identical to those reported from environmental samples, suggesting environmental origin of this azole resistance [25]. Other studies in the neighboring Middle East countries have reported resistance in isolates from environmental settings including Iran and Kuwait with a resistance rate respectively at 12.2% and 7% [22]. The high percentage of azole resistance observed in Europe compared to Asian regions could be explained by environmental factors especially the level of fungicide usage. Indeed, azole fungicides are widely used in agriculture particularly in Europe where its usage is significantly important in the production of vegetables and fruits [26].

In USA, the prevalence of triazole resistance in *Aspergillus fumigatus* isolates is very low due probably to the low usage of azole fungicides. In a multicenter study published in 2014, there were no azole resistances (TR34/L98H mutation) among 1026 isolates tested in 22 states [27]. However, a recent study in USA has reported the first case of the TR34 L98H and TR46 Y121F T289A mutations in *Aspergillus fumigatus* strains [28].

In Africa, reports on azole resistance in *Aspergillus* are very rare. The only cases of resistance of *Aspergillus fumigatus* are detected in isolates from the environment. This is the case in Tanzania where authors have reported 20% of Azole-Resistant *Aspergillus fumigatus* (ARAF) from environmental samples [29]. One of the difficulties explaining the lack of data on azole resistance in *Aspergillus fumigatus* in Africa is the absence of working group addressing these research questions. Another challenge is the lack of appropriate diagnosis platform in the resource-limited settings for the identification of resistant strains.

Azole antifungals are not the only drugs in which resistance has been described. Some *Aspergillus terreus* isolates has been reported to be resistant to amphotericin B [30,31]. This is particularly important as poor clinical response has been

reported in some *Aspergillus terreus* infections. Another species *Aspergillus flavus* has also been found to be resistant to polyenes and voriconazole [32]. These reports emphasize the need to test drug susceptibility in routine laboratory for *Aspergillus* strains implicated in invasive infections for a better surveillance of antifungal drug resistance.

Fusariosis

Species of the genus *Fusarium* are a group of fungi resistant to many antifungals drugs including azoles, echinocandins and polyenes. *Fusarium solani* is the most common species involved

in infections worldwide and the most resistant during *in vitro* testing [33]. This is a major area of concern as this intrinsic resistance is a characteristic of *Fusarium*.

The treatment of *Fusarium* diseases depends on the infected site. Antifungals drugs following surgery are used in 20.6% of cases [34]. However in most of cases including disseminated fusariosis, voriconazole and amphotericin B are recommended as first-line therapy. Unfortunately, several studies have reported the emergence of *in vitro* resistance of *Fusarium* species to these two drugs (Table 2).

Table 2: Antifungal drug resistance of non-dermatophyte molds species.

Species	Country	Resistance rate in %	Sample source	Drugs tested	Reference	
<i>Aspergillus fumigatus</i>	Europe			Azoles	[22]	
	UK	6.6-27.8	Clinical			
	Netherland	3.1-4.6	Clinical			
	Germany	3.2	Clinical			
	Spain	2.5	Clinical			
	Asia					
	India	1.75	Clinical			[24]
	China	27	Clinical			[22]
	Iran	12.2	Environmental			[22]
	Kuwait	7	Environmental			[22]
	Africa					[29]
Tanzania	20	Environmental				
<i>Aspergillus terreus</i>	Austria	-	Clinical and Environmental	Amphotericin B	[31]	
	Spain	27	Clinical		[5]	
<i>Aspergillus flavus</i>	USA	2	Clinical	Voriconazole	[32]	
	Spain	14.8	Clinical	Amphotericin B	[5]	
<i>Fusarium sp</i>	Qatar	-	Clinical	Amphotericin B	[35]	
				Voriconazole		
<i>Fusarium solani</i>	Brazil	-	Clinical	Amphotericin B	[36]	
				Voriconazole		

In Qatar, 39 clinical isolates collected from local and invasive *Fusarium* infections have been demonstrated to be significantly more resistant to amphotericin B, voriconazole and posaconazole using the EUCAST method compared to reference

strains from the CBS-KNAW Fungal Biodiversity Centre [35]. The authors emphasized that this resistant profile associated with a late diagnosis could explain the high mortality rate observed in immunocompromised persons.

Similar results showing amphotericin B and voriconazole resistance in clinical *Fusarium* isolates particularly the *Fusarium solani* species complex have been reported in Brazil [36]. The other antifungal drugs including fluconazole, itraconazole, the echinocandins (micafungin, anidulafungin, and caspofungin) and fluorocytosine have poor activities against members of the genus *Fusarium* [33]. This is the case in India where all 10 clinical isolates from keratitis infections have been reported to be resistant to caspofungin and azoles [37]. Furthermore, many authors have described cross-resistance between itraconazole and fluconazole in one hand and among the three echinocandins in the other hand. Other reports showed potential cross-resistance between azole, echinocandins and polyenes, however without clinical information available. The multidrug resistance profile observed in *Fusarium* species is probably related to the use of azole fungicides in agriculture. Despite the fact that azoles used for plant protection are different to those used clinically, the target site *i.e.*, lanosterol-14 α -demethylase remains the same. Another risk factor is the selective pressure in high-risk patients following antifungal prophylaxis.

Mucormycosis

Management of mucormycosis requires surgical debridement of necrotic tissues followed by antifungal treatment. The liposomal amphotericin B is recommended as the first-line therapy [38] and the period of treatment varies from 6 to 8 weeks according to the resolution of symptoms. In immunocompromised patients, posaconazole is proposed for secondary prophylaxis. Successful treatment depends on several parameters including early diagnosis, prompt administration of the drug and the susceptibility of mucorales to antifungal drugs. However, despite intensive treatments, mucormycosis mortality is still high reaching sometimes 100% according to the clinical form [39]. One of the possible explanations is the limited responses of some members of the group mucorales to antifungal drugs. Although amphotericin B and posaconazole have been demonstrated to be effective *in vitro* to most *Mucorales*, there are some species presenting differential responses to these drugs. For example, amphotericin B gives lower MICs compared with posaconazole against *Mucor circinelloides* while posaconazole MICs are lower against *Cunninghamella bertholletiae* than amphotericin B MICs [40]. The other antifungal drugs including echinocandins, flucytosine, voriconazole and fluconazole have limited *in vitro* activity against the members of the group *Mucorales*.

Conclusion

Antifungal drug resistance in filamentous fungi is increasing worldwide and could complicate the management of patients. It's started to become a public health problem particularly for azole resistance. In Africa, there is a lack of data describing the antifungal drug resistance. So, there is a need for more research and capacity building in this field. The molecular approach coupled with routine screening method like *in vitro* susceptibility testing should be performed for continued international surveillance.

Disclosure of Interest

The authors declare that they have no competing interest.

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