An Overview on Antifungal Resistance

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Abstract:

Fungal infections account for substantial morbidity and mortality worldwide, especially in immunocompromised populations. While antifungal agents such as azoles, echinocandins, and amphotericin B have improved outcomes, increasing resistance among clinically important species poses major therapeutic challenges. Unlike antibacterial resistance, antifungal resistance develops more slowly but is particularly concerning due to the limited number of antifungal drug classes available. Resistance mechanisms include mutations in drug targets, efflux pump overexpression, biofilm formation, and environmental exposure to antifungal agents, particularly in agriculture. The global rise of resistant pathogens highlights the urgent need for enhanced diagnostics, surveillance, and stewardship strategies.

Keywords: Antifungal resistance; Candida auris; Azole resistance; Aspergillus fumigatus; Echinocandins; Antifungal stewardship; Multidrug resistance.

Introduction:

Antifungal resistance has become a critical global health challenge, threatening the effectiveness of the limited antifungal drug classes currently available. Unlike antibacterial therapy, treatment of invasive fungal infections relies mainly on three groups azoles, echinocandins, and polyenes and resistance within these classes significantly restricts therapeutic options **(1).**

The emergence and global spread of *Candida auris* has highlighted the urgency of antifungal resistance. This multidrug-resistant yeast is associated with outbreaks in healthcare settings, shows reduced susceptibility to multiple antifungal classes, and is linked with high mortality rates in vulnerable populations **(2).**

Resistance is not confined to yeasts; molds such as *Aspergillus fumigatus* are increasingly demonstrating azole resistance. Many cases have been attributed to both long-term azole therapy in patients and environmental exposure to azole fungicides, creating a significant public health issue due to cross-resistance **(3).**

At the molecular level, antifungal resistance mechanisms include mutations in target genes such as *ERG11* (azole resistance in *Candida*), *FKS1* (echinocandin resistance in *Candida*

glabrata), and *cyp51A* (azole resistance in *Aspergillus*). Other mechanisms involve efflux pump overexpression, biofilm formation, and adaptive stress responses that reduce drug susceptibility**(4).**

Addressing antifungal resistance requires global surveillance, stewardship of antifungal prescribing, and the development of rapid diagnostics to detect resistance markers early. Promising new antifungal agents including ibrexafungerp and olorofim are currently in development, but sustained investment is essential to expand the therapeutic pipeline **(5).**

Antifungal therapy:

Systemic antifungal therapy is crucial for survival and reduction in morbidity of a wide range of fungal infections, in which some are invasive (invasive aspergillosis and candidaemia), some are chronic (chronic pulmonary aspergillosis and mycetoma), some are allergic (fungal asthma) and a very large number that are superficial (oral or vaginal candidiasis, tinea capitis or corporis (ringworm)). **(6**). (**Table 1**).

Table (1): The current systemic antifungal drugs included on the WHO Essential Medicines **(6)**

Antifungal	Route(s)	Primary indications	Resistance concerns
Fluconazole	Oral, IV	Mucosal candidiasis, prophylaxis in leukemia, HSCT and intensive care, Treatment and maintenance therapy for cryptococosis	All moulds, including Aspergillus resistant. Lower response rates for endemic mycoses such as histoplasmosis. All Candida auris and Candida krusei strains resistant some other species less susceptible or Resistant
Amphotericin B	IV and topical	Invasive candidiasis and cryptococcal meningitis, endemic fungal infections. Empiric therapy in febrile neutropenia. Lower response rate for invasive aspergillosis than azoles	Aspergillus terreus and nidulans resistant. Some strains of Candida auris resistant. Several intrinsically resistant fungi
Flucytosine	Oral, IV	Cryptococcal meningitis, neonatal candidiasis and Candida endocarditis and endophthalmitis, other rare fungal infections	Low levels of resistance in Candida and Cryptococcus. Aspergilli and most moulds and endemic fungi resistan
Itraconazole	Oral, IV	All skin infections, all forms of aspergillosis,	Rising problems with resistance in Aspergillus

		Endemic fungal infections, mucosal candidiasis, prophylaxis in leukaemia	fumigatus, flavus and niger. Some cross resistance with fluconazole in Candida
Voriconazole	Oral, IV	Invasive and chronic aspergillosis, some rare moulds	Some azole cross resistance in Aspergillus. Mucorales intrinsically resistant
Echinocandins (micafungin, caspofungin, anidulafungin)	IV	Candidemia, invasive candiasis, invasive and chronic pulmonary aspergillosis, prophylaxis	Most effective agent for most Candida infections, notably the majority of Candida auris strains. Less effective than azoles for aspergillosis.

HSCT, Hematopoetic Stem Cell Transplant IV, intravenous.

Definition of antifungal resistance:

Antifungal resistance occurs when an antifungal medication no longer works to treat a fungal infection. The fungus can fight off the medicine's effects, in fact treatment failure is a common outcome. This problem is a type of antimicrobial resistance. It occurs when fungi, viruses, bacteria and parasites don't respond to medications developed to treat them. Indeed, your body doesn't develop antifungal resistance, but fungi do **(7)**.

Causes of antifungal resistance:

Antifungal resistance may be intrinsic or acquired (**8).** Genus or species identification often reveals intrinsic resistance such as fluconazole resistance in Candida krusei, amphotericin B resistance in Aspergillus terreus or echinocandin resistance in Cryptococcus species. A tendency for higher rates of acquired resistance is also revealed by species identification, such as fluconazole resistance in Candida glabrata or azole resistance in Aspergillus fumigatus. So fungal identification is critical for good treatment decisions. A guideline on the therapy of rare mould infections has recently been published by the European Confederation of Medical Mycology which addressed therapy for intrinsically resistant mould fungi (**9). (fig 1).**

Fungal resistance mechanisms: (10).

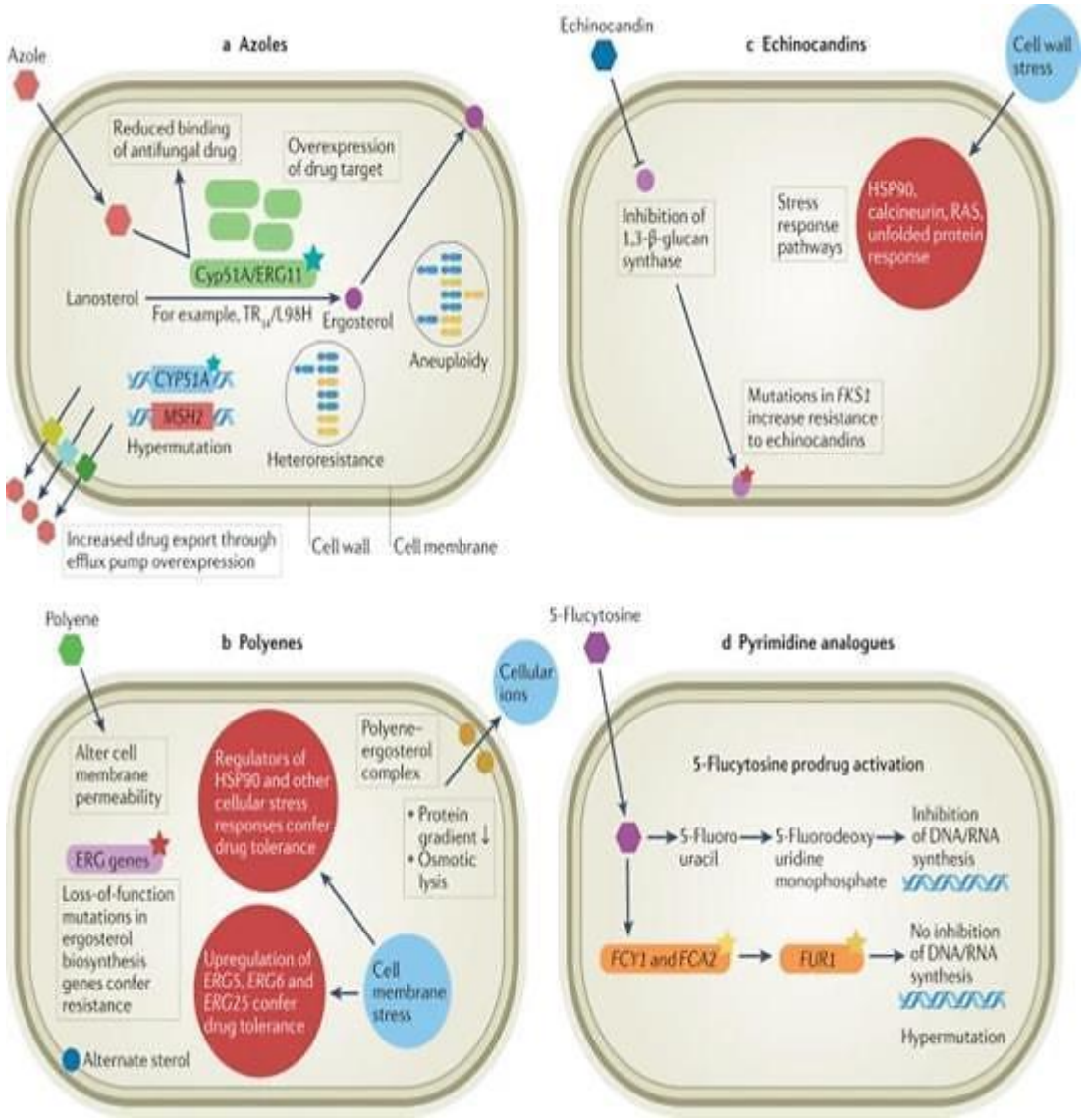

Figure (1): Routes for acquiring antifungal drug resistance **(10).**

Routes to acquire antifungal drug resistance and/or tolerance vary depending on the mode of action (MOA):

(**a**) Azole drug resistance is primarily due to increased efflux of the drug from the fungal cell (particularly in Candida spp.) and modifications to the sterol biosynthesis pathway caused by point mutations and promoter insertions in CYP51A (Aspergillus fumigatus). In other fungal species, such as Cryptococcus neoformans, overexpression of the drug target and efflux pumps caused by chromosomal aneuploidy and hypermutation is common **(11).**

(b) Polyenes alter cell membrane permeability by forming a complex with ergosterol, and resistance is caused by loss-of-function mutations in ergosterol biosynthesis genes (ERG) (particularly in Aspergillus and Candida spp.). In Candida albicans in particular, double loss of ERG3 confers resistance. However, drug tolerance is common, via upregulation of ERG5, ERG6 and ERG25 in C. albicans **(12).**

(c) Cell membrane stress can also impact regulators of Heat shock protein 90 (HSP90), conferring drug tolerance. Echinocandins inhibit 1,3-β-D-glucan synthase (FKS1), and mutations in this gene cause resistance in Candida and Fusarium spp. Echinocandin exposure can also lead to cell wall stress through inhibition of β-glucan synthase, with indirect downstream activation of Ca2+/calcineurin or HSP90/mTOR pathways, which are involved in drug tolerance **(13).**

(**d**) Pyrimidine analogues such as 5-flucytosine inhibit DNA and RNA synthesis. Resistance can arise via point mutations in the target gene FCY1, and is common in Candida spp. Hypermutation in Cryptococcus spp. is also known to cause resistance to this drug class **(14).**

Patients who are at risk for developing antifungal resistance:

Patient populations who are at risk of IFDs are currently expanding and include elder people, those with immune systems compromised by HIV, cancer chemotherapy or transplant-necessitated immune suppression therapy, as well as those with severe viral infections such as influenza virus and COVID-19 **(15).**

This latter group of patients has experienced surges in infection by groups of fungi, notably Aspergillus spp., Candida spp., including C. auris, and in India the Mucoromycota species, which exhibit robust intrinsic and acquired resistance to antifungal treatments **(16)**.

Complications of antifungal resistance:

Certain strains of fungi have become more resistant to antifungal medicines. These fungi continue to multiply and cause infections even when taking medication. A fungus that develops resistance to one drug may not respond to any available treatments, for example, Triazole resistance in Aspergillus fumigatus, most isolates that are resistant, are resistant to at least two

triazoles and most are pan-azole resistant **(17)**, Multi-drug resistant Candida glabrata, Candida auris and other Multi-drug resistant (MDR) Candida species were found **(18).**

Identifying antifungal resistance:

The identification of antifungal resistance has relied on susceptibility testing of cultured microorganisms, identifying Minimum Inhibitory Concentrations (MICs) for specific antimicrobials that, define susceptibility or resistance. There are several methods which are for antifungal susceptibility testing: broth microdilution, disk diffusion, azole agar screening, gradient diffusion and the use of rapid automated instrument. Molecular diagnostic approaches were also been proven **(20)**.

Prevention of antifungal resistance:

All blood and other sterile site cultures of Candida should be identified to species level and susceptibility tested. Stewardship programs should focus in part on stopping unnecessary antifungal therapy for suspected cases of candidiasis and for a positive culture which is not significant (notably respiratory samples). The use of rapid beta 1,3-D- glucan testing can be useful to allow the cessation of therapy as it has a high negative predictive value **(20)**.

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