Antifungals therapeutic failure: Causes beyond steroid abuse

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Abstract
Severity of fungal infection can range from asymptomatic- mild mucocutaneous infections to potentially life threatening systemic disease. Socioeconomic and geoecologic characteristics and increasing number of at risk population are the main determinants of variation in incidence & prevalence of fungal infections. A variety of antifungal drugs are available, but the emerging issue of resistance is of paramount importance. Major factors implicated in Antifungal therapeutic failures and rising incidence of recurrent & relapse include overcrowding, poor hygienic condition, hot & humid climate, self medication, inappropriate and incomplete treatment, undiagnosed uncontrolled diabetes, malnutrition and obviously the issue of rampant steroid abuse.

Keywords: Azoles, Anti fungal.

Introduction
Nearly a billion people have been estimated to have fungal infection of skin, nail, and hair and many 100's of millions have mucosal candidiasis and more than 150 million.[1] people have serious fungal disease which have major impact on their lives, and can even be fatal. Severity of fungal infection can range from asymptomatic- mild mucocutaneous infections to potentially life threatening systemic disease. Socioeconomic and geoecologic characteristics and increasing number of at risk population are the main determinants of variation in incidence & prevalence of fungal infections. A variety of antifungal drugs are available, but the emerging issue of resistance is of paramount importance. Major factors implicated in Antifungal therapeutic failures and rising incidence of recurrent & relapse include overcrowding, poor hygienic condition, hot & humid climate, self medication, inappropriate and incomplete treatment, undiagnosed uncontrolled diabetes, malnutrition and obviously the issue of rampant steroid abuse.

The evolution of drug resistance is an ubiquitous process, where microorganisms try to adapt and compete to survive the environmental stress. Variation in drug resistance can be observed at multiple levels.[2] At species level, fungi can differ in their inherent ability to proliferate during the stress induced by drug exposure, often termed as "tolerance". At population level, fungi can acquire specific mutation that can reduce the inhibitory effect of a drug, referred to as "resistance". The frequency of resistance also varies widely with the class of drug. For example: Polyenes resistance rare.[3] in contrast azole resistance which is by far most prevalent, due to their fungistatic nature that results in strong selective pressure exerted on surviving population. In the clinical settings, a specific type of tolerance referred as "Paradoxical effect" is frequently observed whereby growth of fungus is restored at drug concentration substantially higher than reported MIC. Variation in response to Antifungals exists both in distantly related or closely related species as well as between strains of a species. Variation in resistance among phenotypes are also observed within a population of cells of a single subtype of population.

Biofilms.[4] represents an important example of heterogeneity of drug resistance. Related to their planktionic counterparts, biofilms exhibit remarkable alteration in cellular physiology that confers extreme resistance to antifungals. Biofilms not only offers a refusal from antifungal drugs & host immune response, it also facilitates development of persister cells which are able to tolerate higher concentration of drug. "Persisters"[4] are phenotypic variants that arise in biofilms and are a major factor affecting recalcitrance.

The phenomena of "Hetero-resistance"[4] is another aspect seen in cryptococcus neoformans & Candida albicans where a single cell is capable of giving rise to progeny with heterogeneous resistance, with a small but consistent subset being highly azole resistant. This phenomenon allow resistant population to adapt to increasing concentration of azoles in a stepwise manner with the original susceptibility being restored only after passage through complete absence of drug.

Clinical resistance can be defined as failure to eradicate fungal infection despite administration of antifungal agents with in vitro activity against the same organism. The rising mycological resistance can be reflected by much higher MIC values of various dermatophytes to azoles. The canonical mechanism of antimicrobial resistance evolves as - drug target alteration or overexpression, reduction of intracellular accumulation of drug, or activation of cellular stress response pathway. The main concern of dermatologist in current era is emerging azole resistance.[4]

Azole Resistance
Primary Resistance: Patient acquiring inherently resistant strain from external milieu.
Secondary Resistance: By Mutation- At start of infection the species were susceptible later mutated to develop resistance.
Selection Pressure: Patient harboring a heterogeneous populations and inherently resistant variants are selected

during treatment exposure to azoles. Selection pressure is an important mode of resistance acquired due to exposure of fungal species to sub- MIC levels of various antifungals either from prior clinical exposure to azoles from agricultural source or prior inappropriate treatment. Most of patient with recurrent/relapsing/chronic or recalcitrant tinea give history of multiple and prolonged exposure to various antifungals in past especially topical / oral azoles. Such sub-MIC concentration of drugs not only favours survival of dermatophytes but allows secondary resistance to crop in.

Azoles used in agriculture.[5] also contribute documental in conferring resistance. The most commonly used agricultural preservatives include imidazoles and triazoles, being widely used at preharvest in grain- growing & post harvest phase and also direct application are done to manage evident plant infection. Agricultural azoles are having long term stability and remain for long in ecological niche. The development of cross resistance to triazoles, and relatively higher no. of triazoles used in agriculture than in human infection also affects with their efficacy. This also lead to emergence of plant pathogens as a cause of emerging human infection agents like Colletotrichem graminicola.[5] In a retrospective study By Gupta & Kohli against *T.rubrum* strain in 18 patients with recalcitrant onychomycosis the initial MIC values was 0.125 ug/ml for both Itraconazole and Ketoconazole, which showed a 256 times increase in the value to 32 & 4 ug/ml for both the azoles after 15 month of Antifungal therapy. This post azole exposure increase in the MIC value may be indicative of development of an azole resistance of repeated exposure to azole-known as "CONCEPT OF POTENTIATION OF RESISTANCE"[6] stating that T.rubrum can develop azole resistance after prolonged drug exposure – this may be responsible for azole antifungal failure resulting in recalcitrant and chronic cases.

The key to prevent or at least delay the onset of fungicide resistance in agriculture[5] include preparation of efficient fungicide mixture as well as rotation between fungicides having different modes of action. The recommendation is to maintain highly efficient fungicide, precluding use of mono-fungicide. Acquisition of resistance due to sub-optimal dose or duration of azoles especially itraconazole can confer resistance to other azoles as well, as well as to other antifungals including Terbinafine and Amorolfine. In an in vitro study, it was noted that resistant to all drugs except Ciclopirox olamine[7] emerged at a higher frequency, seen after spontaneous mutation following propagation in culture media with sub- MIC values. Interestingly Itraconazole- resistant mutants; also showed increased MIC values to Amorolfine and Terbinafine beside azoles and enhanced drug efflux is postulated to be the major cause of cross resistance among Antifungals.

The prevalence of mycological azole resistance is as high as 19% in current situation. In contrast to terbinafine, spontaneous mycological resistance is infrequent.[8] Along with it resistance to ciclopirox is still not noted. The concept of invivo-invitro discordance of response to drugs can be elucidated by an interesting " 90-60 rule".[9] It states that infection due to susceptible strain would respond to appropriate therapy in 90% cases, whereas ones due to resistant strain would respond in 60% cases: Factors such as drug pharmacokinetics, drug delivery to site of infection, site of the infection, host immunological response all have their own impact on susceptiblity tests.

Molecular Basis[4,10] of resistance:

a. Drug target over expression/ alteration: This is one of the most common methods. Numerous mutation in azole target gene- ERG11 have been identified adjacent to its enzyme active site. In addition to mutation that reduce the efficacy to target for its inhibitor, increased express of a drug target can also confer resistance, example: gain of function mutation is seen in UPC2 in response to sub MIC value of azole exposure which in turn leads to overexpression of ERG 11 in azole resistant isolates.
b. Reducing intracellular Drug accumulation: ABC transporter-CDR1 and CDR2 are important efflux pumps that are regulated by transcription factor TAC1. Azole resistant variant shows a TAC1 gain of function mutation causing upregulation CDR1 and CDR2. Other important efflux pumps include: MDR1, that are also seen to play role in azole resistance. Another alternative is reducing drug import. Azoles are imported via pH & ATP facilitated diffusion pathways, even these can be altered there by reducing drug import.
c. Regulation of stress Response Pathway: HSP90 is an essential chaperone in eukaryotes that regulates cell signaling. HSP90 promotes Antifungal drug tolerance and evolution of resistance both azoles and echinocandins in various species by stabilizing key regulators of cellular stress responses including calcineurin & PKC1 (Protein kinase C) signaling cascade, MKCl etc. Inhibition of HSP90/ calcineurin/ PKC1 reduces azole and echinocandin resistance in isolates that evolved resistance in human host.
d. Genomic Plasticity: Acquisition of aneuploidy facilitates emergence of resistance to antifungal drugs due to increased dosage of specific resistant determination. Most common one seen in azole resistant species is duplication of Left arm of chromosome 5. In addition changes in copy numbers of entire genome may also prove beneficial for evolution of drug resistance. The scarcity of novel antifungal drugs compared with emergence of resistance is all clinically employed antifungals necessitate identification of strategies to enhance the efficacy of antifungals and block emergence of resistance. Combination therapy is a promising approach. Combining two agents produces increased killing effect, reducing in pathogen population size and thus a further decrease in the probability of acquiring resistant mutation. The enhanced inhibitory effect of combination also allows for lower individual dosing and reduced treatment duration, minimizing host toxicity. Again specific drug combination also have the potential to reverse drug resistance through a process

called as selection inversion. A complimentary approach in developing new therapeutic strategies – is to target proteins that are required for pathogens to grow in the host & their virulence.

For example: pathogenic power of Candida albicans is dependent on its ability of transform between its yeast filamentous morphology. Heat Shock Protein HSP90 is also a key regulator of morphogenesis and can be used as the drug target to combat resistance.

Conclusion

Knowledge and understanding of the mechanism of action and mode of resistance against these antifungals can bring more innovative approaches to be worked upon to efficiently face the emerging hideous aspect of antifungal resistance.

Conflicts of Interest: None.

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How to cite this article: Tiwari Pk, Deb S, Chaudhry RKP, Antifungals therapeutic failure: Causes beyond steroid abuse, *Indian J Clin Exp Dermatol* 2019;5(1):51-53