Original Article

CHANGING PATTERN OF DRUG RESISTANCE IN CANDIDA –A REVIEW

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Abstract

Candidiasis is a most common fungal infection presenting as cutaneous, muco-cutaneous and systemic infection which is caused by over 20 different types of Candida species among which *Candida albicans* is the most common. There is a drastic rise in the fungal infection through out the world, of which the major etiology being Candida species. Azoles are the major class of antifungals used commonly in the clinical practice. Resistance to azoles by various Candida species has increased in recent times. This review will highlight on the importance of identification of fungi and judicious use of appropriate antifungals which will have a greater impact on the clinical outcome.

INTRODUCTION:

There are several classes of antifungal drugs used to treat candida infections. The polyenes, azoles, echinocandins, nucleoside analogues are used depending on the location and the type of infection.[1] Each of these compounds confers varying efficacy. Due to the limited availability of antifungal drugs, Azole group of antifungals were the first line choice and was mostly commonly used to treat candida infections. Azoles like flucanazoles were preferred because as they are cheap , low toxic profile and can be taken orally. But current data documents intrinsic and acquired resistance among many candida species. Many studies have shown the ability of candida species to develop high level resistance to azole antifungals.[2] With the increasing frequency of azole resistant candida isolates it is very important to know the mechanism of such resistance to protect and preserve the azole group of anti fungals. This article elucidates azole resistance *in Candida albicans, Candida dubliniensis, Candida glabarata.*

This review will highlight on various mechanisms involving azole resistance and resistance of different candida species to azole antifungals.[4]

AZOLE RESISTANCE IN CANDIDA.

Azole antifungals inhibits 14-a-sterol demethylase, a key enzyme involved in the synthesis of ergosterol. Consequently cell membrane lacks integrity and accumulation of toxic product occurs through alternate pathway. Azole resistance in Candida occurs by four mechanisms. Mostly by decreased concentration of drug at the target site through efflux pumps in Candida species are which are governed by 2 gene families namely CDR and MDR Genes. In *Candida albicans* there is upregulation of CDR, CDR2, MDR, *in Candida dubliniensis* upregulation of cdCDR, cdMDR and in *Candida glabrata* it is by cg CDR, cgMDR1. Target site alteration due to mutation in ERG11 gene prevents the binding of Azole Antifungal to the enzymatic site. Intrinsic resistance of *Candida krusei* to fluconazole is due to decreased affinity to ERG11 to the drug. Upregulation of target enzyme is achieved by increased gene amplification, increase in transcription rate and decreased degeneration of gene products. Development of bypass pathway where ergosterol is replaced by 14-a-methylfecosterol. Candida species develop resistance to azole antifungals by one or combination of more than one of the above mechanisms.[5-8]

Candida species and their mechanism of azole resistance is illustrated in Table 1.

Table 1: Mechanism of Azole resistance in different Candida species

CANDIDA SPECIES	MECHANISM OF AZOLE RESISTANCE	References
Candida albicans	• Point mutations in ERG11 • Increased expression in ERG11 • Overexpression of drug efflux pump • Mdr1p and Cdr1p/Cdr2p • Inactivation of ERG3(less commonly)	[9,10,11]
Candida glabrata	• Activating mutation in Zinc cluster transcription factor Pdr1 • Formation of petite mutans(Upregulation of Cdr1,Cdr2,SNQ2)	[12,13,14]
Candida krusei	• Reduced affinity Erg11p • Cell membrane changes affecting membrane fluidity • Trisomy in ERG11 chromosomes • Overexpression of drug efflux pump	[15,16,17]
Candida tropicalis	• Expression of MDR1 and cdr1	[18,19]
Candida auris	• Mutation in ERG11 gege • Overexpression of reflux pump	[20]

ALARMING INCREASE IN AZOLE RESISTANCE:

The current decade has witnessed increasing incidence of resistance to azole group of drugs. 20% of *C. albicans* was observed to be resistant to fluconazole and resistances to fluconazole were seen in *C. glabrata* and *C. krusei* in 72% and 100%, respectively. [1] Intrinsic resistance to fluconazole is witnessed in *Candida krusei*, with majority of the isolates showing more than 70%. *C. glabrata* exhibits resistance rate of 15.7% globally. [21] *C. albicans* and few other Candida species namely *C. tropicalis*, and *C. krusei* shown to exhibit secondary resistance. [23] Chowdhry et al study showed 100% resistance to fluconazole and 30% to voricanazole in *Candida auris*. In addition to Azoles it has also been resistance to Amphotericin B and Echinocandins.[23] Cleveland et al study showed 90% resistance to fluconazole, 2% resistance to Echinocandins and 40% resistance to

amphotericin B in *Candida auris*, implicating the development of Multi drug resistance.[24] *C. tropicalis* showed the resistance rates of 11.9% to fluconazole and 9.1% to voriconazole. *C. haemulonii*, a recently identified to cause deadly disease in hospitalised patients. It is also resistant to the Azoles, Amphotericin B, and 5-flucytosine.

CLINICAL IMPLICATION – NEED OF THE HOUR

Identification and speciation is very important in selection of appropriate antifungal which eventually determines the clinical outcome in hospitalised patients. Epidemiological distribution of various species is diverse. Susceptibility also varies according to the species. There is an alarming increase in resistance to the antifungal agents both by *Candida albicans* and non albicans species. But the major concern is many of the isolates that are antifungal resistant simultaneously develop resistance to one or more class of antifungals, which ultimately leads to multi drug resistant organism.

Though majority of the candida species have low level of resistance to echinocandins, there is evidence of coexisting azole and echinocandins resistance in the same isolate.[25] In such case, the therapy should be started with a varying groups like polyenes. Though there is increasing incidence in resistance to echinocandins to candida isolates, the resistance levels are not as high as azoles." IDSA recommends the use of Echinocandins empirically for invasive candidiasis and drug of choice for *C.glabrata* infections."[26] Before putting a patient on treatment we should take into account the prior Echinocandins therapy , recurrence of deep seated fungal infection or prior resistance to azoles. Echinocandins should be targeted in immunosuppressed patients with previous therapy with azoles and also to individuals with *Candida glabrata* infection so as to maintain the dual drug pressure.

CONCLUSION:

A lot of measures have been implemented to avoid the development and widen the level of antifungal resistance. Focus should be done to minimise the impact of immunosuppression. Before enrolling the patient for therapy proper planning should be done to prevent the injudicious drug exposure. Formation of protocols for empirical therapy, strict monitoring of susceptibility pattern in the healthcare settings to find the alterations in the patterns and implement appropriate treatment policies. Treatment failures as a result of developing resistance has led to prolonged hospital stay imposes financial burden. The inherent resistance along with the developing acquired resistance has both ultimately led to major problems in the treatment of Candida infection. This implicates clearly the need for antifungal susceptibility testing including MIC as a routine diagnostic modality.

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