



Emerging Echinocandin Resistance – A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Worldwide there is a steady increase in the number of fungal infections each year. Simultaneously, there is a high rise of antifungal resistance among the *Candida* isolates. This has now become a major concern in hospitalized patients resulting in poor treatment outcome. Echinocandins, a new group of antifungals has given promising results inspite of its increasing rate of resistance exhibited by some *Candida* species.

Keywords: Antifungal resistance; echinocandins; candida species; fungal infections; antifungal drugs; antifungal therapy; fungicidal activity.

1. INTRODUCTION

There is an increasing incidence of fungal infections worldwide [1]. Antifungal therapy is the major treatment option for patients suffering from fungal infections. But treatment options are limited owing to the fewer antifungal drugs and resistance to the existing antifungal drugs. The

increased use of antifungals for candidiasis has led in the development of resistant *Candida* isolates [2]. Azoles antifungals and Amphotericin B are a cornerstone for therapy till now. Toxicities associated with amphotericin and increasing azole resistance have urged the need for an alternative replacement in the management of fungal infections [3].

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Echinocandins, developed over a decade is a milestone in antifungal therapy. Currently, echinocandins are the first line choice for systemic *Candida* infections and a majority of patients with candida blood stream infections are on echinocandin therapy [4,5].

This article will highlight list the available echinocandin drugs available, their mode of action, the acquired resistance mechanisms and its clinical implications.

2. ECHINOCANDINS – NEW CLASS OF ANTIFUNGALS

Three echinocandin antifungal drugs caspofungin, micafungin, and anidulafungin are available over a decade. The echinocandins have a distinctive mechanism of action, suppressing the action of [1,3]-D-glucan synthase [6]. Echinocandins have been used in invasive candidiasis. In addition, caspofungin is used in febrile neutropenia and invasive aspergillosis, and is safe for use in pediatric patients [7]. Micafungin is the only echinocandin used in bone marrow transplantation [8].

2.1 Spectrum of Activity

Echinocandins exhibit good fungicidal activities against candida spp mainly *Candida albicans*, *Candida parapsilosis* and *Candida guilliermondii*

.Good activity is also shown against amphotericin B-resistant and fluconazole-resistant *Candida glabrata* [9,10]. For Aspergillus species, echinocandins have fungistatic activity in contrast to amphotericin B and triazoles, which exhibit fungicidal activity. Echinocandin resistance, though not common, has been reported in *C. glabrata* and *C. parapsilosis* [11,12].

2.2 Criteria and Cutoff for Resistance

Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have established standardized microbroth dilution susceptibility tests for *Candida* and echinocandins which show uniformly potent activity against most *Candida* species”[13-15]. “Both CLSI and EUCAST have confirmed species and drug- specific clinical breakpoints (CBP) for echinocandin drugs and epidemiological cutoff values have been defined for anidulafungin and micafungin

against common *Candida* species”[16-19]. “EUCAST has not established caspofungin breakpoint and does not recommend caspofungin E test for MIC detection or sensititre yeast only system for clinical assessment, owing to high interlaboratory testing variability and the CLSI has raised caution when using caspofungin testing, especially with *C. glabrata*”[20,21]. Many of the candida isolates showing resistant to caspofungin were susceptible to anidulafungin and micafungin [21,22].owing to this EUCAST has gauged anidulafungin and micafungin as markers for caspofungin susceptibility [23,24].

2.3 Acquired Resistance Mechanisms

2.3.1 FKS mechanism of resistance

Aminoacid alteration in the Fks subunits of glucan synthase causes echinocandin resistance [25]. “Mutations are highly confined to Phe641– Pro649 and Arg1361 (*C. albicans* equivalent) and/or equivalent regions of *FKS2* in *C. glabrata* [26,27]”. “Amino acid substitutions in Fks subunits induce elevated MIC values (10–100 fold) and reduce the sensitivity of glucan synthase (IC50) to drug by as much as 3000- fold”[28]. Amino acid alterations are more frequent in Fks 2 than Fks 1 [26,29,30]. These mutations in Fks region alter the pharmaco dynamic profile of the drug [31,32].In *C. albicans*, changes at position Ser645 is the most common resistant pattern noticed [29]. In *C. glabrata*, mutations are common in *FKS1* and *FKS2*. “Changes located at Ser663 (equivalent to *C. albicans* Ser645) in Fks2 is the commonest” [28,33].other interchanges at Ser629 in Fks1 and Phe659 in Fks2 also result in treatment failure [34]. “Other hot-spot mutations may confer phenotypic resistance, but escalating drug doses are more effective against resistant strains harboring such mutations”[35]. Presence of mutations in Fks 1 or Fks 2 along with the gene expressions determines the resistance [30,36,37]. *C. tropicalis*, *C. krusei* and *C. kefyr* confer resistance to echinocandins by Fks mechanism [38,39].

2.3.2 Hot spot diversity

Mutation at Phe641 and Ser645 in *C. albicans* is most commonly noticed compared to the C-terminal end of hot spot 1, which is less commonly noticed [30,40,41]. Diversity at Pro649 in the *C. parapsilosis* and at Met633 and

Ala634 in *C. guilliermondii*, causes increased MIC values [42]. Infecting strains with intrinsically reduced susceptibility carries an uncertain clinical significance [43,44]. The sensitivity of glutan synthase for echinocandins is lower in candida parasilopsis than candida albicans which causes high MIC value. "But the enzyme, while less sensitive, is still inhibited at typical therapeutic drug concentrations, which accounts for clinical response" [45]. "Mutations at the third region W695 (outside clinical hot spots 1 and 2) of Saccharomyces cerevisiae Fks1 is found but does not cause treatment failure"[46].

2.3.3 Biofilms

Biofilms are "a thin but robust layer of mucilage adhering irreversibly to a solid surface, inert material ,or living tissue producing extracellular polymers that provide a structural matrix and contain a community of bacteria and other microorganisms [47,48]". *Candida* species have inherent tendency to form biofilms . The beta 1,3 D glucan a component of biofilm matrix seizes the drug and allows less concentration at cellular level [49]. Alteration of the transcriptional regulators like R1m and Smi1 and changes in the Fks alter the glutan synthesis which in turn leads to the formation of biofilms conferring resistance [50].

2.3.4 Adaptive cellular factors

All fungi possess various factors to overcome cellular stress. On encountering a cellular stress there is increased MIC level of the drug which does not always correlate with treatment response [25]. This is the preliminary state for Fks mechanism of resistance and in turn lead to full blown resistance. Fungal stress adaptive pathways lead to increased production of chitin as a compensatory mechanism leading to resistance [51]. This acts at the level of cell wall. Changes in the cell membrane level can also alter the activity of echinocandin. Alteration in the sphingolipid synthesis and composition alters the efficacy of caspofungin and micafungin [52].

2.3.5 Hsp90

Heat shock proteins are "a family of proteins that are produced by cells in response to exposure to stressful conditions [53]". Hsp90 changes are not only associated with azole resistance but also with echinocandin resistance. Any reduction in the function of Hsp90 causes resistance in *C. albicans*, *C. glabrata*, and *A. fumigates* [54,55].

Hsp90 confers resistance to echinocandins by calcineurin and Mkc1. Inhibition of Hsp90 activity increases the efficacy and activity of echinocandins. This clearly suggests Hsp90 acts as a target to increase the potency of echinocandins [56].

Echinocandin Drug Resistance	
Mechanism of Resistance	Fungal species
FKS	<i>C.albicans</i> , <i>C.glabrata</i> , <i>C. tropicalis</i> , <i>C. krusei</i> and <i>C. kefyri</i>
Heat Shock Protein 90	<i>C.albicans</i> , <i>C. glabrata</i> , and <i>A.fumigatus</i>
Hot Spot Diversity	<i>C. parapsilosis</i> , <i>C. guilliermondii</i>
Biofilm	All <i>Candida</i> species

2.4 Clinical Implications

A huge population of patients suffering from systemic fungal infections do not respond to antifungal therapy due to acquired drug resistance [57]. *In vivo* success therapy with antifungal drugs was found to be less than 75% compared to the invitro susceptibility testing results indicating invitro results are alone cannot predict treatment outcome [58,59].

Though in recent times there is emergence of echinocandin resistant candida species, resistance noticed in candida albicans and some of the other candida spp is still low varying from 2-3%. Contrary to this the level of resistance in *Candida glabrata* is very high ranging from 8-13%. Increased use of echinocandin for *Candida glabrata* infections has alarmingly increased resistance from 3% to >13 [60,61]. In many cases these echinocandin resistant isolates are also azole resistant leading to multidrug resistant candida spp imposing a treatment challenge [62].

3. CONCLUSION

Echinocandins in contrast to the other class of antifungals possess several unique merits. When choosing such a drug for patient therapy the treating physician should take in to account the metabolism and drug interaction, the dose, duration to be prescribed and their recommended indications

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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