Popular Article

ANTIFUNGAL RESISTANCE IN ANIMALS: A BRIEF NOTE

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ABSTRACT

Fungi play significant roles in causing diseases across various organisms within both the plant and animal realms, encompassing humans as well. Due to the widespread use of antifungals in both agricultural practices and modern medical treatments, the incidence of resistant fungal infections has been increasing. The challenge of escalating antifungal resistance is worsened by the lack of new antifungal agents under development, especially those with distinctive mechanisms of action. Antifungal resistance in veterinary medicine is also a growing concern, yet comprehensive data on animal fungal infections remains scarce. This paper explores the limited array of antifungal drugs, mechanisms underlying resistance, and strategies to combat this issue.

Keywords: Anti-fungal resistance, animals, histoplasmosis, therapy, mechanisms

I. INTRODUCTION

Fungi, being multicellular, eukaryotic organisms, are widespread both in the environment and within organisms. Due to their opportunistic nature, they can also lead to infections, ranging from minor health issues such as yeast infections and ringworm to potentially fatal conditions like Aspergillosis, Mucormycosis, and Histoplasmosis. Presently, only a limited array of antifungal drugs is available for treatment. Over time, certain strains of fungi have developed resistance to multiple classes of antifungals. Information about the prevalence of fungal infections and antifungal resistance in veterinary medicine is relatively rare. Resistance levels can greatly differ depending on the animal species, geographic location, and methodologies utilized for in vitro susceptibility testing. One significant drawback of such investigations is their typically small sample sizes, particularly when compared to similar studies focusing on human isolates. Moreover, the antifungal susceptibility testing of veterinary isolates is often done using non-standardized methods, including variations in antifungal panels, incubation times and temperatures, minimum inhibitory concentration (MIC) endpoints, and more, further complicating the direct comparison of results across studies. As a result, the true impact of antifungal resistance on animal health and agricultural systems remains largely unknown.

II. ANTI-FUNGAL THERAPY

In the field of veterinary medicine, the range of available antifungal drugs for treatment remains remarkably restricted. There are five major classes of systemic antifungal agents: polyenes, azoles, allylamines, nucleoside analogues, and echinocandins. Among these categories, polyenes and azoles are the most commonly used antifungal drugs for animals. However, amphotericin B, nystatin, and pimaricin (natamycin) are the only polyene macrolides administered in veterinary medicine. Among the azole group of drugs, Miconazole has a wide antifungal spectrum against most fungi and yeasts of veterinary interest. Ketoconazole has an antifungal spectrum similar to that of miconazole. Itraconazole and fluconazole are the most active drugs of the antifungal triazoles. Cost considerations often hinder access to newer antifungal drugs, rendering them impractical for standard

veterinary practice. Even when off-patent alternatives become accessible, their suitability for extended therapy may be limited, leading to the discontinuation of treatment before complete clinical recovery. Additionally, administering antifungal drugs to specific animal species, particularly wild animals, may induce stress or other complications requiring careful management.

For whatever reason, when a limited number of antifungal drugs are employed, susceptible fungi may be eliminated by these medications, leaving behind strains with varying degrees of resistance. Consequently, these resistant strains can propagate, resulting in a surge in their populations. In addition to this, Antifungal resistance can emerge in clinical settings either through extended treatment periods or via the selection of resistant strains following prolonged exposure to sublethal concentrations of compounds in the environment, and often due to widespread fungicide usage in various sectors such as agriculture, material preservation, and farm facility sanitation. Additionally, certain fungi inherently exhibit resistance to specific antifungal agents.

III. MECHANISM OF RESISTANCE

In general, both primary and adaptive mechanisms of antifungal drug resistance have been recognized so far. Adaptive resistance mechanisms include alterations in drug targets, such as their modification or overexpression, heightened activity of multidrug transporters, and the triggering of stress responses within fungal cells. Inherent resistance (also known as primary resistance) is employed to characterize species wherein all identified isolates inherently possess resistance to a specific antifungal. Additionally, the formation of biofilms significantly contributes to the emergence and persistence of antifungal resistance. Irrespective of its source, antifungal resistance has the potential to exacerbate clinical outcomes and, in severe cases, lead to treatment failure. The common mechanisms of occurrence of antifungal resistance are described in the following figure (**Fig. 1**).

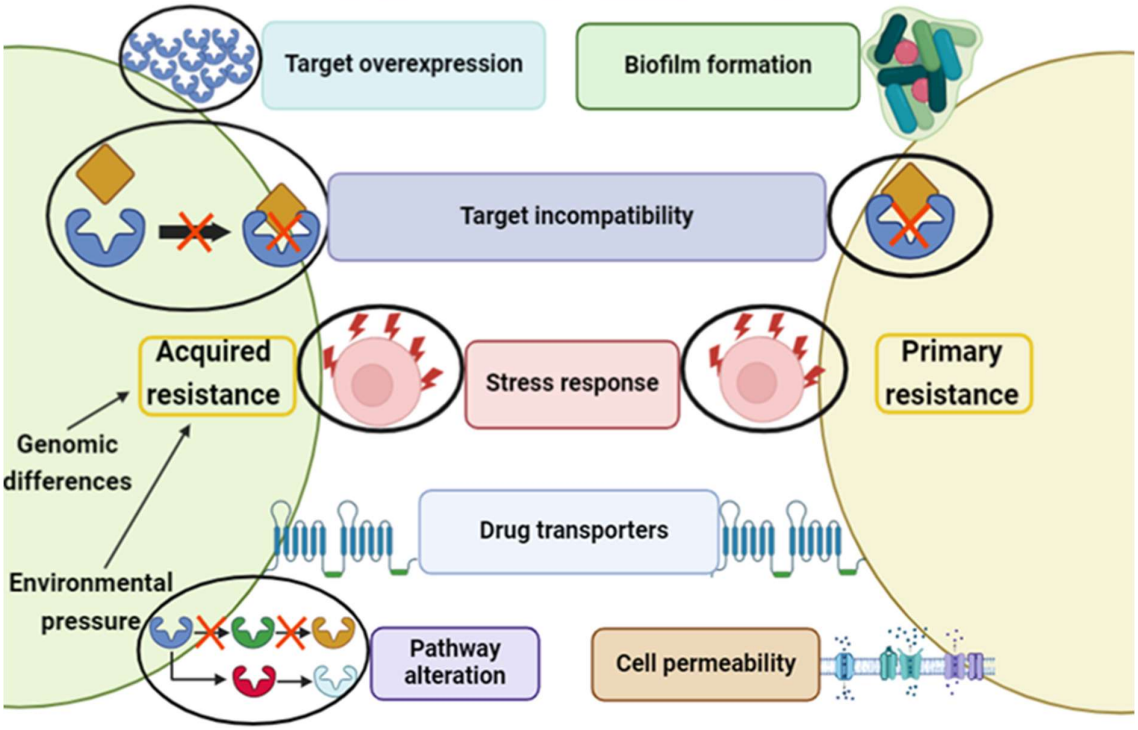

Fig. 1: The Common Mechanisms of Occurrence of Antifungal Resistance

IV. FUNGAL RESISTANCE TO POLYENE MACROLIDE ANTIMICROBIALS

Fungi often develop resistance to polyene antifungals by altering the binding site of their target (ergosterol) which is crucial for maintaining membrane integrity and fluidity. However, fungal cells have limited capacity to modify this target. Common resistance mechanisms include the absence of ergosterol in the cell membrane, often due to mutations in ERG3 or ERG6, or a decrease in ergosterol levels within the fungal cells. Polyene macrolides inherently exhibit resistance against dermatophytes, and the development of resistance to these antifungals is rare, both clinically and in the laboratory environment. Pythium, a pseudo fungus, shows reduced susceptibility because of its low ergosterol content, which serves as the drug's target within its membranes. While resistance has been noted in Candida species, it typically evolves slowly and seldom reaches significant levels, even with prolonged treatment.

V. FUNGAL RESISTANCE TO AZOLES

Resistance to azole antifungals can emerge due to various factors such as reduced drug uptake, alterations in intracellular drug processing, changes in the target enzymes, modifications in other enzymes involved in the ergosterol biosynthetic pathway, or adjustments in efflux pumps. Clinical strains of Candida and Aspergillus organisms have been increasingly exhibiting resistance to azoles through diverse mechanisms. The up-regulation of ABC [Adenosine triphosphate (ATP)-binding cassette] family transporters like CDR1 and CDR2 leads to enhanced drug efflux. Mutations in the ERG11 gene, responsible for encoding lanosterol demethylase, result in changes affecting the binding of azole drugs to their target sites. Elevated expression of major facilitator transporters contributes to decreased intracellular accumulation of azoles. Instances of resistance development to itraconazole and fluconazole have been observed in strains isolated from equine uterine cultures. Fluconazole resistance has been reported in clinical isolates of *C. neoformans*. As for *Aspergillus fumigatus* isolates from dogs and cats, there is presently no evidence of azole resistance; however, cases of resistance to itraconazole and voriconazole have been reported in avian *A. fumigatus* strains in Europe.

VI. RESISTANCE TO ALLYLAMINES AND FLUOROPYRIMIDINES

Resistance to allylamine is uncommon, but these medications may be susceptible to multidrug resistance efflux mechanisms. Resistance to flucytosine can rapidly emerge, even during treatment, rendering it unsuitable as the sole therapy for fungal infections. The precise mechanisms of resistance remain incompletely explained; however, they might require deficiencies in cytosine permease or changes in metabolic enzymes to develop resistance.

VII. APPROACHES TO TACKLE ANTIFUNGAL RESISTANCE

Defined strategies for preventing and managing the emergence of antifungal resistance are yet to be established, although insights from combating antibacterial resistance could be instructive. These strategies encompass the prudent use of antifungal medications, ensuring appropriate dosing to avoid suboptimal levels, administering the most suitable antifungal agents, and conducting surveillance studies to accurately gauge the prevalence of antifungal drug resistance. Several experimental antifungal compounds are presently undergoing evaluation in preclinical and clinical settings. While these agents share similarities with existing antifungal classes in terms of their mechanisms of action, they may offer distinct advantages. Conventional antifungal medications typically target fungal cell walls and membranes, distinctive features of these microorganisms. So, identifying novel drug targets represents a promising avenue for combating resistance. An

encouraging therapeutic strategy to enhance antifungal drug efficacy and counter the emergence of resistant fungi involves employing drug combinations. Antimicrobial Peptides (AMPs) hold significant promise as alternatives to traditional antifungal medications. The primary mechanism of action involves disrupting the membranes of fungal cells through electrostatic and hydrophobic interactions, leading to the leakage of intracellular contents. This physicochemical mechanism reduces the likelihood of resistance development, as repairing damaged membranes is inefficient. Additionally, AMPs possess multiple mechanisms for attacking pathogens, augmenting the likelihood of successful treatment.

VIII. CONCLUSION

Fungal infections present substantial hurdles due to the limited treatment options available and the rise of resistant strains. Veterinary medicine faces its own set of challenges, including constrained drug availability and inadequate information on infection prevalence and resistance patterns. To combat these issues, it is crucial to prioritize prevention strategies, and new antifungal drug development, explore alternative targeting approaches, utilize combination therapies, and investigate the potential of antimicrobial peptides. Collaboration across disciplines is essential for effectively managing fungal infections in both human and veterinary settings. By addressing surveillance gaps, promoting treatment advancements, and executing precise preventive measures, we can alleviate the impacts of antifungal resistance on animal health leading to promoting public health.

IX. REFERENCES

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