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Review Article

ANTIFUNGAL RESISTANCE OF FEW *ASPERGILLUS* SPECIES

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ABSTRACT

Aspergillus species cause a wide range of diseases including allergic syndromes, chronic pulmonary and nasal sinus aspergillosis and acute and sub acute invasive disease. Resistance of *Aspergilli* to some clinically used antifungal brings a worrying clinical prognostic in people attacked by aspergillosis. The number of fundamentally different types of antifungal agents that are available for treatment remains extremely limited. Currently there are four classes of antifungal agents with activity against *Aspergillus*. Resistance in *Aspergillus* is emerging but the data on the antifungal compounds are limited compared to other fungal species. In this paper summarized some known antifungal drugs against diseased causing *Aspergillus* species.

Keywords: *Aspergillus*, Aspergillosis, Antifungal agents.

INTRODUCTION

One of the oldest named genera of fungi, *Aspergillus* received its name from Micheli in 1729. *Aspergillus* species are widely distributed in the environment and are often found in association with rotting vegetation. They are also opportunistic pathogens of humans that can cause primary invasive lung infections and disseminate to other organs. The important identifying characteristics of the species *A. niger* group bear black spores; the *A. ochraceus* group is yellow to brown, while *A. fumigatus*, *A. nidulans*, and *A. flavus* are green and many more.

Their spores can be present in high concentrations in the atmosphere, and *Aspergillus* species grow rapidly at elevated temperatures (% 40°C). These attributes, together with the weak defenses of the immunocompromised host, are considered the main reasons for their pathogenicity, rather than specific virulence traits.[1]

Aspergillus species cause a wide range of diseases including allergic syndromes, chronic pulmonary and nasal sinus aspergillosis and acute and sub acute invasive disease. *Aspergillus fumigatus* is the most common species of *Aspergillus* that causes life-threatening pulmonary disease in severely immunocompromised patients.[2] Invasive aspergillosis is an infectious disease that is difficult to manage. Resistance of *Aspergilli* to some clinically used antifungals brings a worrying clinical prognostic in people attacked by aspergillosis.[3,4] For over fifty years

antibiotics have been applied for treating or inhibiting infections. The wide use and sometimes misuse of chemo-antimicrobials in both human and animal medicine has been responsible for the selection of resistant strains.[5,6] The evolution of resistance to antimicrobial agents that are used to control pathogens in medicine and agriculture is a well-documented problem. In fungi, the evolution of drug resistance is more likely to proceed by the sequential accumulation of adaptive mutations.[7] Although antifungal-drug resistance does not seem to be as much of a problem as resistance to antibacterial agents in bacteria[8] one long-term concern is that the number of fundamentally different types of antifungal agents that are available for treatment remains extremely limited. Over the past decade, the incidence of serious infections caused by opportunistic fungal pathogens has increased dramatically due to alterations in the immune status of patients. Unfortunately, the widespread use of triazole antifungal agents to combat these infections has led to the emergence of clinically significant drug resistance that limits therapy and emphasizes the need for a better understanding of the molecular mechanisms conferring drug resistance. Microbiological resistance can be defined as a shift (i.e. a decrease) in antifungal drug susceptibility that can be measured *in vitro* by appropriate laboratory methods. Various formats have been developed to test the susceptibility of Aspergilli; including macro/micro broth dilution, disc diffusion and E test.[9] The distinction between a susceptible and a resistant fungal isolate can be made when a threshold drug susceptibility value (i.e. the breakpoint MIC, for *M*inimal *I*nhibitory *C*oncentration) is reached. Whereas antifungal-drug resistance is usually quantified using the minimum inhibitory concentration (MIC), in which growth in the presence of a range of drug concentrations is measured over a defined time period according to a standard protocol.[10] The lowest drug concentration that results in a significant reduction of growth (usually either 50% or 90% reduction of growth compared with growth in the absence of the drug) is the MIC. An improved MIC determination has led to more reproducible and accurate detection of resistance, which has benefited the study of resistance mechanisms. MIC values of a given fungal pathogen for a specific drug is less relevant for the microbiologist or the molecular biologist, since only a modest shift of antifungal drug susceptibility measured by increase in MIC values can be the consequence of one or several cellular alterations linked to modifications of the genetic material.

Currently there are four classes of antifungal agents with activity against *Aspergillus*: the polyenes, such as Amphotericin B deoxycholate (AMB), its lipid formulations, and nystatin (including liposomal nystatin); the triazoles, including itraconazole (ITC), the recently introduced voriconazole (VRC)and the investigational posaconazole (POS); the echinocandins, such as caspofungin (CAS), the recently introduced micafungin (MICA) and the investigational anidulafungin; and the allylamines such as Terbinafine (TRB).[11,12,13] Amphotericin B has limited activity against *A. terreus*[14,15,16] and *A. nidulans*.[17] while *A. calidoustus* (previously known as *A. ustus*) appears to be intrinsically resistant to triazole compounds.[18] Posaconazole is a potent extended-spectrum triazole shown to have activity *in vitro* and in animal studies against *Aspergillu* spp., including amphotericin B-resistant *A. terreus*.[19, 20, 21] Furthermore, several species in the *A. fumigatus* complex (*A. lentulus, A. pseudofisheri* and *A fumigatiaffinis*) appear to be intrinsically resistant to azoles, and in the case of *A. lentulus* and *A. fumigatiaffinis* resistant to amphotericin B as well.[22] Recently reported the rapid emergence of azole resistance in *A. fumigatus* isolates cultured from patients with invasive aspergillosis.[23,24] Azole resistance has emerged since 1999 in clinical *A. fumigatus* isolates from Dutch hospitals, and 6· 0-12· 8 %

of patients were found to harbour an azole-resistant isolate.[25] Azole resistance has predominantly been reported for *A. fumigatus*, the species which accounts for approximately 80% of invasive infections.[26] Yet itraconazole resistance has also been detected in other species in the *Fumigati* section such as *A. lentulus* and *Neosartorya pseudofi scheri*[27], as well as species in other taxonomic sections including *A. niger*, *A.terreus* and *A. flavus*.[28,29] Most of the susceptibility data relates to itraconazole, although increasing reports describe resistance to the newer azole agents including posaconazole and voriconazole. The first cases of itraconazole resistance were from the late 1980s[30], yet the vast majorities have been detected since the turn of the millennium. The frequency is largely undefined, as many centres do not routinely test the susceptibility of their aspergilla isolates. Resistance has currently been reported in Belgium, Canada, China, Denmark, France, Norway, Spain, Sweden, The Netherlands, UK and the USA. Much less is known regarding acquired resistance to echinocandins. Caspofungin is licensed for salvage treatment of invasive aspergillosis and is recommended as second line treatment by the IDSA (Infectious Diseases Society of America).[31] Fluconazole and ketoconazole (KCZ) are inactive against *Aspergillus*. Further development with newer antifungal drugs and interpretative breakpoints will continue this process.

CONCLUSION

Resistance in *Aspergillus* is emerging and the data on the antifungal compounds are limited compared to other fungal species. This review will summarize the present situation of antifungal drugs diseased causing *Aspergillus* species.

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