Antifungal Resistance: It Is Time to Look Outside the Box

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Dear Editor,

Bacteria are certainly a huge global concern, but antifungal drug resistance is a growing global concern in terms of both newly developing species that are resistant to various antifungal treatments and novel resistant versions of previously susceptible infections.[1]

Antifungals have historically been excluded from antimicrobial resistance (AMR) efforts due to the widespread underestimation of the hazards posed by fungi to public health, which is further complicated by the biological distinctions between bacterial and fungal diseases.[2] A bottomless supply of new diseases and varieties of long-standing adversaries that quickly adapt and evolve when exposed to antifungal agents are also guaranteed by the vastness and diversity of the fungal kingdom.[1]

Increasing environmental resistance is anticipated to have an impact on the clinical management of fungal infections due to the close link that exists between fungal populations in the environment and subsequent exposure to antifungals. As phytopathogenic fungi quickly adapt and constantly develop resistance to the variety of fungicides used to control them, agribusinesses must constantly innovate by creating new chemicals or modifying their current fungicides to prevent resistance from building up.[1]

Humans can have a wide range of diseases from fungal allergies to invasive fungal diseases that can be fatal. Over two million individuals worldwide suffer from invasive fungal diseases, which currently cause more fatalities each year than malaria or tuberculosis combined.[1] Despite the development of novel antifungals, the mortality rate from invasive fungal disease is typically higher (>50%) than that from bacterial disease.[3]

Treatment has traditionally mainly relied on four kinds of systemically active antifungal medications: azoles, echinocandins, polyenes, and 5-flucytosine, an analogue of pyrimidine. Nonetheless, fungi react quickly to chemical assault, and treatment failure is frequently the result. This breakdown can be linked to a combination of fungal traits such as different cell morphologies, antifungal tolerance, and resistance, as well as underlying immunological deficiencies in the host and antifungal medication properties.[1]

The lack of sensitive and targeted diagnostic tests, the absence of clinically calibrated antifungal susceptibility testing, and the restricted range of antifungal medication classes present challenges to a clinician's capacity to manage drug-resistant invasive fungal diseases (IFDs) today.[1] To maintain our existing choice of antifungal drugs, antifungal stewardship will need to take precedence over antimicrobial stewardship programs once again. Quick diagnostics can aid in stewardship efforts by reducing the amount of time needed to decide if a patient needs an antifungal medication.[3]

To develop effective treatment plans to address the growing issue of antifungal resistance, we must expand our understanding of the molecular mechanisms by which fungi adapt to the challenge of antifungal exposure. There are several antifungal resistance pathways. For example, drug target gene mutations in *FKS1* in *Candida, Cryptococcus*, and *Aspergillus* are the main cause of echinocandin resistance. Mutations have been found in *FKS1* and its paralog *FKS2* for *Candida glabrata*.

Mutations in the drug target (*ERG11*), target overexpression, or efflux pump can result in azole resistance. Gene plasticity and cellular stress responses are other methods of resistance among many.[4]

These problems cannot be resolved by concentrating only on one aspect. A comprehensive strategy is required, giving each component the weight it deserves. When it comes to AMR control, the ABCs of any undertaking should be applied with attention to antifungal stewardship: advocacy (A), capacity building (B), and community participation (C).[5]

These are not distinct elements and have the power to affect the creation and execution of actions related to the other elements. A vicious circle of general weakness in national efforts against AFR is initiated by weakness in any one of these

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components. The formation of policies and programs, along with the active involvement of communities to ensure their willing participation, proper financial support, and a thorough strengthening of multisectoral capability, are all brought about by the advocacy and dedication of political leadership. A nation possessing robust capabilities and technical expertise will have a stronger professional voice when lobbying legislators to prioritize AFR and step-up national initiatives. Demanding timely and efficient action from the national authorities is necessary to lessen Antifungal Resistance (AFR).[5]

A more concerted international response is required for networks, infrastructures, research funding, and career development. Policymakers, funding agencies, researchers, and antifungal manufacturers and users must all work together to address these issues.

Combination strategies to combat invasive fungal infections. Compared with monotherapy, treatment with drug combinations can improve drug efficacy and overcome resistance. Targeting resistance mechanism to improve antifungal efficacy and increased bioavailability against multidrug-resistant pathogens.

Among the antifungal agents under development are olorofim, which inhibits the synthesis of pyrimidines de novo; fosmanogepix, which blocks the production of glycosylphosphatidylinositol (GPI); and ibrexafungerp, which inhibits glucan synthesis through a mechanism different from that of echinocandins. Furthermore, there are several agents within the current classes of antifungal drugs that have been found to have improved pharmacokinetics and safety; these include the tetrazole oteseconazole, which has a higher specificity for the fungal CYP51 enzyme and a longer half-life, and the echinocandin rezafungin.[4]

In addition to improving the efficacy of currently available medications, high-throughput screening of compound libraries in conjunction with chemical genomic resources in fungal infections can aid in the identification of compounds that can strengthen the antifungal pipeline and promote the creation of resistance-aversive treatments.

Continued efforts to increase our understanding of the mechanisms underlying antifungal resistance will undoubtedly help therapeutic approaches to invasive fungal infections.

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