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ANTIFUNGAL THERAPY: PROBLEMS AND PROSPECTS

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Introduction. Modern medical progress has a significant pace compared to what happened even 10 years ago, so there is a problem of increasing the number of patients with weakened immunity, which leads to an increase in the number of clinically significant fungal infections. Drugs with a fungicidal or fungistatic effect are used for the treatment of fungal infections. The constant use of antifungal drugs has resulted in the development of drug resistance to them.

Very few new antifungal drugs have been developed in recent decades because the costs of developing new drugs are too high and the risks of not bringing them to the commercialization stage are too great. New antifungal agents are in short supply on the market for the same reason as antibiotics - funding for such research is very limited, investors prefer drugs for chronic diseases that patients take all their lives, rather than those that will cure the infection and become «unnecessary». There is no big incentive, there is no big market but there is a huge need for new antifungals.

Objective. There is a variety of antifungal drugs on the market. The most effective and safe drug choice for a particular patient is an important aspect of medical practice.

Materials and methods. A study of literary sources devoted to the current state of research, the creation, properties and features of the use of antifungal drugs, in particular dosage forms containing antifungal agents, in clinical practice, problems of the rational use of antifungal drugs and resistance, as well as areas of combating microbial resistance and the creation of innovative antifungal agents.

Results. An analysis of the main groups of antifungal drugs is necessary to understand the specifics of their use and prescription. In clinical practice, systemic treatment of fungal infections relies on four main classes of drugs that target three different fungal metabolic pathways: fluoropyrimidines, polyenes, azoles, and echinocandins. Other classes of drugs, such as morpholines and allylamines, are typically limited to topical use due to lack of efficacy or serious side effects with systemic administration.

Classification and mechanism of antifungal drugs action.

The majority of modern antifungal agents target the synthesis of ergosterol or directly interact with it. Ergosterol is a key component of the fungal cell membrane, regulating its fluidity, asymmetry, and overall integrity. Antifungal drugs are classified based on their chemical structure, which influences their spectrum of activity and pharmacokinetic profiles in treating various fungal infections.

- Azoles: Their main target is the heme protein that catalyzes the cytochrome P-450-dependent 14-demethylation of lanosterol. This action depletes ergosterol and causes an accumulation of sterol precursors, ultimately changing the structure and function of the plasma membrane. Azole derivatives include imidazoles (e.g., Ketoconazole, Clotrimazole) and triazoles (e.g., Fluconazole, Itraconazole).

- Polyenes: These drugs interact directly with the membrane sterol to form structurally altered aqueous pores. This process drastically increases membrane permeability, leading to the leakage of vital cytoplasmic components and subsequent organism death.
- Allylamines: These agents inhibit the early stages of ergosterol biosynthesis by blocking the enzyme squalene epoxidase. Fungal cell death is primarily attributed to the accumulation of squalene, which can increase membrane permeability and disrupt cellular organization, rather than ergosterol deficiency itself.
- Echinocandins: These compounds target the fungal cell wall by acting as non-competitive inhibitors of β -(1,3)-glucan synthase. This mechanism causes severe cellular and ultrastructural changes, including cell wall thickening and inability of cell separation, making the cells osmotically sensitive.
- 5-Fluorocytosine: This agent inhibits nucleic acid synthesis by interfering with pyrimidine metabolism, which affects the synthesis of RNA, DNA, and protein in the fungal cell. Due to widespread primary resistance, it is generally combined with other antifungals like Amphotericin B or Fluconazole.
- Griseofulvin: This natural antifungal was the first oral drug approved for dermatophytosis. Its action involves disrupting microtubule cellular proteins, leading to mitotic arrest, which impairs the fungal cell's ability to reproduce. It also binds to keratin in the skin, hair, and nails, rendering the new tissue resistant to fungal infection as the infected tissue is shed.

The emergence of resistance highlights the importance of selecting the appropriate drug, often necessitating a sensitivity test of the pathogen before treatment begins.

The primary challenge in antifungal therapy is the toxicity of drugs to the human body and the increasing emergence of resistant fungal strains. Research is continuously focused on identifying new mechanisms of action and developing new pharmaceutical agents:

- MGCD290: An antifungal inhibitor of the fungal histone deacetylase Hos2 (HDAC). It exhibits synergy *in vitro* with azoles, even against resistant strains, effectively reducing the minimum inhibitory concentration.
- SCY-078: Distinct from conventional echinocandins, this agent has demonstrated potency against *Candida* and *Aspergillus* species, including strains resistant to both azoles and echinocandins, but shows poor activity against *Mucor* and *Fusarium* infections.
- APX001: A first-in-class prodrug whose active form, manogepix, targets the enzyme inositol acyltransferase (Gwt1). This enzyme is crucial for maintaining the structural integrity of the fungal cell wall and facilitating pathogen attachment to host cells.
- F901318 (Olorofim): An orotomidione compound that specifically targets fungal dihydroorotate dehydrogenase. It has shown low toxicity in mammalian cells and is currently in Phase 2 clinical trials for prophylactic use.

On the ukrainian pharmaceutical market the assortment of antifungal drugs is extensive, including domestic and imported preparations. The total number of

antifungal drug trade names is 236. Imported products are supplied from 29 countries, with the main importers being India, Italy, and Germany.

Globally, the consumption of antifungal drugs is increasing, particularly in middle-income countries. Consumption patterns, especially for triazoles and ketoconazole, reflect evolving epidemiology of resistance and changes in global health policy. Life-saving agents like echinocandins and polyenes may be underutilized in middle-income countries, while high-income countries often have earlier access to new drugs under development. Coordinated global and national health policy efforts are necessary to effectively address the growing threat posed by increasingly prevalent and drug-resistant fungal pathogens.

Conclusion. The landscape of antifungal therapy is defined by its reliance on a limited number of drug classes (polyenes, azoles, echinocandins, and fluoropyrimidines) that target a few key fungal metabolic pathways, primarily ergosterol biosynthesis and cell wall integrity. While these classes provide the foundation for systemic treatment, the field faces significant challenges due to the growing global threat of antifungal resistance and the inherent toxicity of existing agents to human hosts.

In summary, effective management of fungal infections requires not only the continued development of novel, safer, and more potent agents but also coordinated global and national health policy efforts to ensure timely and equitable access to necessary diagnostics and existing, as well as emerging, life-saving antifungal therapies worldwide.

Key words: antifungal drugs, ergosterol, azoles, resistance, toxicity.