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Fungal Foes: Role of Antifungal Resistance in Animal Health

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Introduction:

One new global concern is antimicrobial resistance (AMR). Fungi are multicellular, eukaryotic organisms that are ubiquitous in the environment and body—research indicates that fungi account for ~0.1% of the human gut microbiome. Fungi can be harmless and even helpful when used as food (e.g. mushrooms, yeast, etc.) and pharmaceuticals (penicillin). However, due to their opportunistic nature, fungi can also cause infections, ranging in severity from inconvenient (yeast infection, ringworm/athletes' foot, etc.) to deadly (Aspergillosis, Mucormycosis, Histoplasmosis, etc.). Organizations such as the WHO and the U.S. Centers for Disease Control and Prevention (CDC) have designated a number of invasive disease-causing fungi as emerging concerns.

Antifungal Resistance Driven:

According to agencies like the WHO and the U.S. Centers for Disease Control and Prevention (CDC), a number of invasive disease-causing fungi are considered emergent hazards. For instance, the clinically significant pathogen Candida auris, which causes candidiasis (particularly in immunocompromised individuals), has developed resistance to numerous antifungal medications, such as fluconazole and amphotericin B. C. auris has a 39% mortality rate as a result, and the CDC has labeled it an "urgent concern". The Aspergillus genus of fungus is another important source of worry. A. fumigatus is a common environmental mold that can cause aspergillosis, a condition that affects the lungs and respiratory system. Since the 1990s, A. fumigatus has demonstrated an increase in azole resistance, leading to treatment failures and its inclusion on the CDC's "watch list."

Key Drivers Contributing to Antifungal Resistance:

Human medicine:

→ **Excessive prescribing and misuse**: Offering antifungals when they are unnecessary or administering incorrect dosages or treatment lengths.

→ **Incomplete treatment courses:** Discontinuing medication too soon permits the remaining fungi to grow and acquire resistance.

→ **Insufficient new medications:** The small variety of efficient antifungal categories leads to the reliance on existing drugs over more extended periods, intensifying selection pressure.

→ **Pre-existing health issues:** Individuals with weakened immune defenses, such as those affected by HIV/AIDS, cancer, or organ transplants, have an increased risk of severe fungal infections, and prolonged treatment can promote resistance.

Agriculture:

→ **Widespread fungicide application:** Similar substances that serve as antifungals for humans are heavily utilized in agriculture to safeguard crops and in livestock farming.

→ **Environmental contamination:** The pervasive application of fungicides in the environment imposes pressure for resistance to develop among fungal populations, which can later spread and infect people.

Climate change:

→ **Increasing fungal environments:** Climate change may facilitate the geographical expansion of certain fungal pathogens and the rise of new species.

Types of Antifungal Agents:

Current antifungal medications comprise various classes: polyenes such as amphotericin B, azoles like fluconazole and voriconazole, echinocandins such as caspofungin, and antimetabolites like flucytosine. Each class acts by focusing on distinct parts of the fungal cell, including the cell membrane, cell wall, or nucleic acid production. Additional classes include allylamines (such as terbinafine) and morpholines.

Key Classes of Antifungal Agents:

- **Polyenes:** These antifungals, like amphotericin B, bind to ergosterol in the fungal cell membrane, creating pores that cause cell contents to leak out.
- **Azoles:** This broad class includes fluconazole, itraconazole, and voriconazole. They work by inhibiting an enzyme (lanosterol 14-α-demethylase) needed to synthesize ergosterol, disrupting the fungal cell membrane's structure and function.
- **Echinocandins:** Examples include caspofungin, micafungin, and anidulafungin. They inhibit the synthesis of (1,3)-D-glucan, a key component of the fungal cell wall.
- **Antimetabolites:** Flucytosine (-fluorocytosine) is converted inside the fungus to a compound that inhibits both DNA and RNA synthesis.
- **Allylamines and morpholines:** Allylamines, such as terbinafine and naftifine, inhibit squalene epoxidase, an enzyme in the ergosterol synthesis pathway.
- **Other agents:** Other compounds include griseofulvin, which inhibits cell division by binding to

tubulin, and undecylenic acid.

Mode of Action in Details:

Antifungal Class	Molecular Target	Mechanism of Action
Polyenes	Membrane ergosterol	Binds to ergosterol, forms pores in the cell membrane, causing leakage of intracellular components.
Azoles	lanosterol 14-α-demethylase	Inhibits ergosterol synthesis, disrupting membrane integrity.
Echinocandins	(1,3)-D-glucan synthase	Inhibits the synthesis of (1,3)-D-glucan, a major component of the fungal cell wall, leading to cell wall damage.
Antimetabolites	DNA and RNA synthesis	Converted intracellularly to 5-fluorouracil, which inhibits DNA and RNA synthesis.
Allylamines	Squalene epoxidase	Inhibits ergosterol synthesis at an earlier point, leading to the accumulation of toxic squalene.

Challenges to Antifungal Drug Development:

Challenges to antifungal drug development include the high rate of resistance, the similarity between fungal and human cells (making selective toxicity difficult), the limited pipeline of new drugs, and the adverse side effects of existing medications. Fungi can develop resistance through mechanisms like target site modifications and the upregulation of efflux pumps, and environmental and agricultural use of fungicides can contribute to this problem.

Key Challenges:

- **Drug resistance:** Fungi can adapt to resist current medications, often evolving quicker than novel treatments can be identified. Mechanisms of this include alterations to drug targets, heightened activity of efflux pumps that expel medications, and various other metabolic changes. The emergence of resistance is driven by conditions such as excessive use of drugs, which applies selection pressure.
- **Eukaryotic similarity:** The structure of fungal cells is akin to that of human cells, causing challenges in the development of medications that eliminate the fungus without causing harm to the host.
- **Limited drug in pipeline:** There is a lack of new categories of antifungal medications, and the rate of creating new options has been sluggish.
- **Adverse side effects:** Numerous current antifungals are accompanied by significant adverse reactions, including kidney toxicity or liver injury, restricting their application.
- **Limited spectrum:** Certain antifungal medications are effective only against a limited variety of fungi, and the rise of resistance can diminish the efficacy of available drugs.
- **Difficult development process:** The lengthy and resource-heavy development path entails obstacles such as defining relevant pharmacodynamic targets, anticipating human metabolites, and scaling up

production.

What Can Be Done to Stop the Spread of Antifungal Resistance?

To halt the advancement of antifungal resistance, individuals should adhere to their complete antifungal prescriptions and maintain proper hygiene to reduce the risk of fungal infections. Healthcare professionals must prescribe antifungals carefully, use diagnostic assessments to direct treatment protocols, and observe patterns of resistance. At a systemic level, collaboration is crucial, including adopting a One Health strategy that integrates human, animal, and environmental health, alongside continuous research for new medications and diagnostic technologies.

For patients and the public:

- ***Complete antifungal regimen:*** Always finish the prescribed medication course, even if symptoms improve.
- ***Fungal infection prevention:*** Maintain good hygiene practices, such as keeping skin dry, particularly in warm and humid areas.
- ***Avoid sharing items:*** Refrain from sharing personal belongings like towels, combs, or hairbrushes.
- ***Hand hygiene:*** Wash your hands often, especially when in healthcare facilities.
- ***Responsible disposal of medication:*** Adhere to proper procedures for discarding unused or expired antifungal medications.

For healthcare professionals:

- ***Prescribing with caution:*** Only issue antifungals when absolutely needed and refrain from unnecessary prescriptions.
- ***Utilize diagnostics:*** Conduct tests for fungal infections prior to treatment and check for resistance if the initial therapy does not succeed.
- ***Monitor prescriptions:*** Record the dosage, treatment duration, and rationale for each antifungal prescription.
- ***Stay updated:*** Keep informed about local and community patterns of antifungal resistance.

For researchers, policymakers and institutions:

- ***Establish stewardship programs:*** Integrate antifungal administration within antimicrobial stewardship initiatives in healthcare establishments.
- ***Enhance monitoring:*** Leverage tracking and various technologies to oversee the proliferation of resistant strains in both medical and agricultural environments.
- ***Fund research and development:*** Invest in understanding how resistance arises and in the creation of new antifungal medications targeting different mechanisms.
- ***Refine diagnostics:*** Create and validate new diagnostic tests that can swiftly identify emerging resistant strains.

- ***Encourage collaboration:*** Promote partnerships across human, animal, and plant health domains through the One Health framework**.**

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