Advances in Pharmacology and Therapeutics Journal
Shahid Sadoughi University of Medical Sciences, Yazd, Iran

SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES

letter to editor

Development of Drug Resistance in the Treatment of Systemic Candidiasis: New Challenges and Future Solutions

Running Title: Drug Resistance in Systemic Candidiasis, New Challenges

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ARTICLEINFO

Received: 07/18/2026

Accepted: 07/20/2026

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Abstract

Systemic candidiasis continues to be the most prevalent healthcare-associated invasive fungal infection, contributing significantly with a high mortality. While *Candida albicans* continues to be the predominant causative agent, other species such as *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, and various rare Candida species exhibit resistance to fluconazole and other triazole antifungals. The increasing prevalence of fluconazole-resistant *C. parapsilosis*, echinocandin-resistant *C. glabrata*, and a new reported multidrug-resistant species, *Candida auris*, has made clinical management more challenging. Effective antifungal treatment must be chosen based on patient-specific factors, the severity of the disease, history of antifungal use, local epidemiological data, organ involvement, the presence of indwelling medical devices, and accurate species identification. Currently, the challenges associated with antifungal treatments comprise the slow diagnosis reducing from traditional culture techniques and the restricted application of rapid diagnostic tools in clinical settings. To resolve these challenges, it is essential to develop innovative antifungal agents, improve stewardship programs, and enhance global resistance monitoring to maximize treatment results and maintain the effectiveness of antifungal therapies.

Keywords: Systemic Candidiasis, Antifungal Agents , Drug Resistance

Citation: Jafari Nodoushan A.A. Development of Drug Resistance in the Treatment of Systemic Candidiasis: New Challenges and Future Solutions. Adv Pharmacol Ther J. 2026;6(1): 3-5

Introduction

Candidiasis caused by Candida species is a common fungal infection that can range from superficial to severe and, in its invasive form, threaten life. Systemic candidiasis has remained a challenge in therapy, though there has been great progress in antifungal drug therapy. Invasive candidiasis has remained associated with considerable morbidity and mortality, particularly in critically ill patients who are immunosuppressed (1). Although azoles, echinocandins, and polyenes remain the mainstays of treatment, the rising problem of drug resistance has begun to affect their efficacy (2).

There has been a marked shift in Candida infections from Candida albicans to other non-albicans species, such as *Candida tropicalis*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and a newly emerged drug-resistant species, *Candida auris*. These pathogens are either intrinsically resistant or have developed drug resistance to antifungal medications such as fluconazole (3).

Among these non-albicans species, *Candida auris*, first identified in Japan in 2009 (4), has been a major concern for the global community over the past decade due to its rapid emergence and spread. As a result, with the increasing number of cases of immunocompromised patients, *Candida auris* has become one of the primary concerns in critical care medicine, with high morbidity and mortality rates, accounting for about 13 million infections, including 1.5 million deaths annually worldwide (5).

In pharmacology, drug-resistant infections arise from various causes, including mutations in drug-target enzymes, overexpression of efflux pumps, and adaptive changes in sterol biosynthesis (6).

Current Challenges and Future Directions in Antifungal Therapy

Biofilm-related infections also contribute to antifungal drug resistance by inhibiting drug penetration and increasing tolerance to fungicidal doses (7). This issue is especially significant in invasive candidiasis involving medical devices, given the pharmacokinetic and pharmacodynamic properties of currently used antifungals (8). Suboptimal antifungal therapy and treatment duration also drive selective pressure and accelerate resistance (9).

Beyond resistance, current challenges also extend to diagnosis. Classic culture techniques often delay diagnosis, postponing treatment initiation and worsening outcomes, particularly among newborns. While new techniques and biomarkers promise earlier diagnosis, their implementation in pharmacotherapeutic practice remains limited (10).

To overcome these challenges, there is an urgent need for innovative pharmacological and therapeutic approaches. Next-generation antifungal drugs should target novel fungal pathways, including cell wall integrity, mitochondrial metabolism, and virulence factor regulation. Combination therapy may also yield synergistic effects, but this area needs strong validation (11).

Antifungal stewardship programs should integrate pharmacokinetic and pharmacodynamic properties, susceptibility data, and patient-specific dosing regimens. These programs can optimize antifungal exposure, minimize unjustified use, and maintain the effectiveness of existing drugs. Improving global resistance surveillance and fostering collaboration among pharmacologists, microbiologists, and

  DOI: https://doi.org/10.18502/aptj.v6i1.???

physicians will also strengthen monitoring and management strategies (10).

Conclusion

Overall, antifungal resistance in systemic candidiasis is an emerging issue with significant pharmacological and medical implications. Long-term research and development of antifungal medicines and innovative therapies are urgently needed to provide efficacious treatment for invasive infections caused by Candida species.

Sincerely

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Acknowledgments: We hereby thank the Clinical Research Development Unit of medical school for their kind cooperation.

Conflict of Interest There isn't competing interests concerning authorship and/or publication of this article**.**

Funding: No funding was received for this work.

Ethical considerations: No human participants, animals, or identifiable personal data were involved in this work; therefore, ethical approval was not required.

code IR.BMSU.REC.1403.039.

Authors' contribution: The author solely conceived, wrote, revised, and approved the final version of the manuscript.

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