

Tolerance and heteroresistance to echinocandins in *Candida auris*: conceptual issues, clinical implications, and outstanding questions

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ABSTRACT *Candida auris* is a significant public health threat due to its environmental persistence and multidrug resistance, with echinocandins being the preferred treatment. However, in addition to resistance, echinocandin tolerance and heteroresistance may contribute to treatment challenges. Echinocandin tolerance involves reduced drug-mediated killing, while heteroresistance is the ability of a small cell subset to grow at high drug concentrations. These phenomena may facilitate the emergence of full resistance and complicate clinical outcomes. The clinical significance of these mechanisms remains unclear, with limited data correlating them with treatment failures. Research is needed to understand their mechanisms and impact, develop streamlined and robust methods to detect them in clinical settings, and explore mitigation strategies. The pathogen's range of drug adaptations demands innovative approaches like spatial transcriptomics to dissect these complex responses and improve patient outcomes.

KEYWORDS *Candida auris*, echinocandins, heteroresistance, tolerance

When *Candida auris* emerged as a new fungal pathogen over 15 years ago, it posed challenges similar to infections by other *Candida* species while exhibiting additional unique characteristics that rapidly made it a significant public health concern. Like other major *Candida* pathogens, *C. auris* forms robust biofilms on medical devices (e.g., catheters), shielding it from antifungals and immune attacks, contributing to persistent and often severe invasive infections, especially in highly vulnerable patients with comorbidities, frailties, and immunosuppression (1, 2). Additionally, it can manipulate host immune mechanisms, particularly innate immunity, to evade detection and hinder the body's ability to clear infections (3). *C. auris* can also switch between different morphologies (yeast, filamentous forms, and pseudohyphae) to adapt to host environments (4, 5). Finally, it is capable of tremendous genetic plasticity, whereby it can rapidly evolve under stress, acquiring large-scale chromosomal changes (e.g., rearrangements and aneuploidies) and point mutations that enhance survival following exposure to antifungals and immune responses (6–8).

Moreover, in addition to all these already troublesome features that are shared by other *Candida* pathogens, *C. auris* possesses several distinct traits that further complicate its treatment and eradication. First, several clades of *C. auris* can exhibit resistance to multiple classes of antifungal drugs, including azoles, echinocandins, and polyenes, sometimes without a significant fitness cost in the host (9), leaving physicians with limited to no treatment options (10). Second, a distinctive phenotype exhibited by certain isolates of *C. auris* is their ability to form aggregates, and this has been linked to immune evasion, adhesion, and pathogenesis, even environmental persistence (11). We note that some debate remains regarding the role of cell aggregation in *C. auris* because heterogeneous results have been obtained depending on the experimental

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model and site of infection, with strain-to-strain variability and geographic origin/genetic clade as additional important confounders (12–17). Third, the high transmissibility of *C. auris*, coupled with the ineffectiveness of standard cleaning measures with many commonly used hospital disinfectants, including quaternary ammonium compounds, creates a “perfect storm” for its persistence in healthcare environments and its role in hard-to-control, widespread healthcare outbreaks (18). This is compounded by the fact that, unlike other *Candida* species, *C. auris* can survive for weeks to months on dry surfaces, contributing to spread (19, 20). Finally, *C. auris* exhibits unusually high tolerance to other stresses, such as high temperatures (up to 42°C) and high salt concentrations (20), enabling it to persist in environments with high salt concentrations, such as the skin.

C. auris high stress tolerance translates to its ability to withstand the action of multiple antifungal agents with different modes of action. Among the three major antifungal drug classes used for systemic infections, *C. auris* shows the lowest levels of resistance against echinocandins (ranging from 0% to 8%) (21), which are, therefore, the preferred treatment option. Echinocandins act by inhibiting the essential cell wall-building enzyme 1,3- β -glucan synthase and, unlike azoles, are fungicidal in *Candida* species. Echinocandin resistance (primary and acquired) has been described in multiple species, including *C. auris*, and is due to mutations in 1,3- β -glucan synthase *FKS* genes (22–24). However, in addition to frank resistance, defined as the ability to grow well above a certain drug concentration, two additional mechanisms have been recently identified *in vitro* and implicated as contributing to *C. auris* ability to survive in the presence of echinocandins—tolerance and heteroresistance. Both echinocandin tolerance and heteroresistance are characterized by increased fungal cell survival in the presence of what should be a fungicidal drug and are defined as follows.

Echinocandin tolerance

Tolerance *in vitro* is generally thought of as a transient, non-genetically encoded phenomenon, and its definition depends on whether a drug is cidal or static. Antifungal drug tolerance has been predominantly studied in the context of azole antifungals, which are static in *Candida* species, and for which tolerance is usually defined as the ability to grow slowly above the minimal inhibitory concentration (MIC) (25–28). However, for cidal drugs such as echinocandins, a more appropriate definition is the one used for bactericidal antibiotics, in which tolerance is defined as reduced or delayed cell killing above the MIC (i.e., producing a killing curve with a shallower slope) (29). This slowed killing can be a characteristic either of a large part of the population or a small subset of cells, which are typically referred to as “persisters.” Although no *in vitro* echinocandin kill curve data for *C. auris* have been published, there is a strong suggestion that echinocandins might not be as cidal *in vivo*, i.e., in host tissues. For instance, in a murine model of systemic *C. auris* infection, treatment with various echinocandins significantly reduced but did not sterilize infected tissues (kidneys, hearts, and brains), resulting in residual drug-tolerant *C. auris* loads ranging from hundreds to millions of CFUs (30). Mechanistically, the limited *in vitro* studies on echinocandin tolerance in *C. albicans* have revealed a role in the transcriptional upregulation of cell wall stress responses, resulting in a compensatory increase in cell wall chitin levels (31). Furthermore, also in *C. albicans*, the acquisition of echinocandin or fluconazole tolerance has been associated with chromosomal alterations, specifically full or segmental aneuploidies (28, 31, 32). Another phenomenon, which may be thought of as a type of tolerance, is known as paradoxical growth or the “eagle effect,” whereby cells are inhibited at normal MIC concentrations but paradoxically are able to grow at supra-MIC concentrations. Although the paradoxical effect has been described for *C. auris* and echinocandins (22), its mechanisms, while likely associated with tolerance, are unknown.

Echinocandin heteroresistance

Unlike tolerance, heteroresistance is defined similarly for static and cidal drugs as the ability of a small subset of the population to grow (e.g., form colonies) on a medium

containing above-MIC drug concentrations. Because resistance is also defined based on growth at high drug concentrations, heteroresistance can be thought of as phenotypic resistance of a small subset of the population. In fungi, heteroresistance to azoles has been observed in several *Candida* and *Cryptococcus* species (33–36), and in *C. glabrata*, it was associated with an increased drug efflux capacity (36). On the other hand, heteroresistance to echinocandins (specifically, micafungin) has, thus far, been reported only in *C. parapsilosis* and *C. auris* (37). The mechanisms leading to echinocandin heteroresistance are not understood; because it is a phenomenon exhibited by a small subpopulation of presumably genetically identical cells, it may have an epigenetic basis. However, chromosomal number variations, i.e., aneuploidies, have been implicated in azole heteroresistance in *C. albicans* and *C. neoformans* (34, 35, 38).

The clinical significance of echinocandin tolerance and heteroresistance is unknown. Thus far, the role of fluconazole tolerance in therapeutic failures has been implied in *C. albicans* and *C. glabrata* (25, 27, 39), but no correlation between tolerance to echinocandins and their *in vivo* (36) efficacy has yet been reported. In *C. auris*, isolates exhibiting paradoxical growth in caspofungin *in vitro* have been examined in a mouse model of systemic candidiasis and were found to be as susceptible to caspofungin treatment as isolates incapable of paradoxical growth (22). Echinocandin heteroresistance was found to be associated with an increased risk of *C. parapsilosis* breakthrough bloodstream infections during micafungin prophylaxis in patients with allogeneic stem cell transplantation (37). However, it is still unclear if heteroresistance by itself would explain these breakthrough infections; *C. parapsilosis* notably has an innately elevated echinocandin MIC relative to other *Candida* species due to a naturally occurring *FKS1* hot-spot polymorphism, which makes the therapeutic window much narrower and may be an additional factor increasing the risk of breakthrough infections.

In Box 1, we list some outstanding basic, translational, and clinical research questions related to echinocandin tolerance and heteroresistance that would be valuable to address in *Candida* in general and *C. auris* in particular.

BOX 1. OUTSTANDING QUESTIONS REGARDING THE TRANSLATIONAL AND CLINICAL IMPLICATIONS OF ECHINOCANDIN TOLERANCE AND HETERORESISTANCE IN *C. AURIS*

- Since more cells are alive and available to acquire genetic mutations both in echinocandin tolerance and heteroresistance, are these phenomena stepping stones for the emergence of full-blown resistance? If so, what are the molecular mechanisms?
- Are *Candida* strains that are echinocandin-heteroresistant also more echinocandin-tolerant and *vice versa*? If so, what are the molecular underpinnings?
- Are there any fitness trade-offs associated with echinocandin tolerance and/or heteroresistance?
- How much variability in frequency and magnitude of echinocandin tolerance and/or heteroresistance exists within strains and various *Candida* species that exhibit conventional susceptibility or non-susceptibility to echinocandins?
- Are there echinocandin-specific (caspofungin, micafungin, and anidulafungin) differences in frequency and magnitude of echinocandin tolerance and/or heteroresistance?
- Does exposure of *Candida* to a new generation of echinocandins with long half-life (i.e., rezafungin) and high C_{\max} /MIC alter the frequency and magnitude of echinocandin tolerance and/or heteroresistance?
- Is there an association between echinocandin tolerance and/or heteroresistance and *Candida* morphogenesis (as it has been described with *C. auris* tolerance to azoles [40]) and virulence?

- Could one expect tolerance and/or heteroresistance with new first-in-class agents that have novel mechanisms of action (e.g., fosmanogepix)?
- As monotherapy induces stress adaptation, would combinations of two cidal drugs (e.g., amphotericin B and echinocandins) or other antifungal adjuvants (e.g., chloroquine or nikkomycin) abrogate echinocandin tolerance and/or heteroresistance (41–43)?
- Can artificial intelligence be used to “predict” tolerance and resistance based, for example, on clinical parameters and whole-genome sequencing of *Candida* isolates (37)?
- Can methods be developed to detect, in a time-efficient and practicable way, echinocandin tolerance and/or heteroresistance in the clinical laboratory (33)?
- Can highly multiplexed spatial single-cell transcriptomics, as recently described in bacteria (44), dissect the complex mechanisms of diverse and heterogeneous responses of *C. auris* to echinocandins on a population level?
- Is echinocandin tolerance and/or heteroresistance in *Candida* more prevalent in complex polymicrobial environments (e.g., in biofilms or gut mucosa)?
- Can optimization of echinocandin pharmacokinetics in settings associated with lower drug exposures (e.g., gastrointestinal mucosal surfaces), high volume of distribution in critically ill patients in ICU (45), and biofilms mitigate echinocandin tolerance and/or heteroresistance?

In conclusion, the responses of *Candida* to a cidal drug such as an echinocandin might be more complex and heterogeneous than previously thought, and this is certainly the case for the multidrug-resistant emerging pathogen *C. auris*. Those dynamic and diverse responses are probably amplified in the complex *in vivo* microenvironment of tissue infections (e.g., various and fluctuating iron and nutrient availability, O₂/CO₂ concentrations [46], immune cells, albumin, polymicrobial communities, and biofilms) and cannot be easily captured by current conventional *in vitro* tests. As many population-level susceptibility phenotypes in *Candida* are driven by heterogeneous responses adapted by single cells, more efforts are needed to develop sensitive, high-throughput multiplex spatial transcriptomic methods (44) to dissect those phenotypes and uncover the metabolic strategies driving these phenotypes. Clinicians should be reminded that *Candida*, especially *C. auris*, is a highly sophisticated and nimble pathogen with tremendous adaptability and capacity to resist killing.

Finally, the emerging complexities of phenotypes *in vitro* as relating to the *in vivo* capability of cidal drugs such as the echinocandins underscores the complexities of *in vitro*–*in vivo* correlations and outcomes in candidiasis (47). Typically, failure of an antifungal is multifactorial, MICs do not reflect the whole story (47), and heteroresistance and/or tolerance, which are nearly impossible to detect in most clinical microbiology labs, might underlie some of these failures despite apparently “low” MICs. As is the case in infection in general, pharmacokinetics/pharmacodynamics play key roles (48), especially for pathogenic species such as *C. auris* that have innately high MICs and propensity for tolerance/heteroresistance. In the big picture, within the setting of persistent infection and in view of the tremendous genomic versatility of *Candida*, a range of echinocandin non-susceptible phenotypes might be operative, which can be associated with enhanced virulence traits (immune evasion properties, biofilm formation, and pathogenicity), as it has been shown recently in patients with refractory *C. albicans* fungemia (49).


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REFERENCES

1. Sherry L, Ramage G, Kean R, Borman A, Johnson EM, Richardson MD, Rautemaa-Richardson R. 2017. Biofilm-forming capability of highly virulent, multidrug-resistant *Candida auris*. *Emerg Infect Dis* 23:328–331. <https://doi.org/10.3201/eid2302.161320>

2. Singh R, Kaur M, Chakrabarti A, Shankarnarayan SA, Rudramurthy SM. 2019. Biofilm formation by *Candida auris* isolated from colonising sites and candidemia cases. *Mycoses* 62:706–709. <https://doi.org/10.1111/myc.12947>

3. Holt AM, Nett JE. 2024. Innate immune response to *Candida auris*. *Curr Opin Microbiol* 80:102510. <https://doi.org/10.1016/j.mib.2024.102510>

4. Bryak G, Cox A, Lionakis MS, Thangamani S. 2024. Yeast and filamentous *Candida auris* stimulate distinct immune responses in the skin. *mSphere* 9:e00055-24. <https://doi.org/10.1128/msphere.00055-24>

5. Fan S, Yue H, Zheng Q, Bing J, Tian S, Chen J, Ennis CL, Nobile CJ, Huang G, Du H. 2021. Filamentous growth is a general feature of *Candida auris* clinical isolates. *Med Mycol* 59:734–740. <https://doi.org/10.1093/mmy/m yaa116>

6. Bravo Ruiz G, Ross ZK, Holmes E, Schelenz S, Gow NAR, Lorenz A. 2019. Rapid and extensive karyotype diversification in haploid clinical *Candida auris* isolates. *Curr Genet* 65:1217–1228. <https://doi.org/10.1007/s00294-019-00976-w>

7. Burrack LS, Todd RT, Soisangwan N, Wiederhold NP, Selmecki A. 2022. Genomic diversity across *Candida auris* clinical isolates shapes rapid development of antifungal resistance. *mBio* 13:e00842-22. <https://doi.org/10.1128/mbio.00842-22>

8. Muñoz JF, Welsh RM, Shea T, Batra D, Gade L, Howard D, Rowe LA, Meis JF, Litvintseva AP, Cuomo CA. 2021. Clade-specific chromosomal rearrangements and loss of subtelomeric adhesins in *Candida auris*. *Genetics* 218:iyab029. <https://doi.org/10.1093/genetics/iyab029>

9. Carolus H, Sofras D, Boccarella G, Sephton-Clark P, Biriukov V, Cauldron NC, Lobo Romero C, Vergauwen R, Yazdani S, Pierson S, Jacobs S, Vandecruys P, Wijnants S, Meis JF, Gabaldón T, van den Berg P, Rybak JM, Cuomo CA, Van Dijck P. 2024. Acquired amphotericin B resistance leads to fitness trade-offs that can be mitigated by compensatory

evolution in *Candida auris*. *Nat Microbiol* 9:3304–3320. <https://doi.org/10.1038/s41564-024-01854-z>

10. Rybak JM, Cuomo CA, Rogers PD. 2022. The molecular and genetic basis of antifungal resistance in the emerging fungal pathogen *Candida auris*. *Curr Opin Microbiol* 70:102208. <https://doi.org/10.1016/j.mib.2022.102208>

11. Short B, Brown J, Delaney C, Sherry L, Williams C, Ramage G, Kean R. 2019. *Candida auris* exhibits resilient biofilm characteristics *in vitro*: implications for environmental persistence. *J Hosp Infect* 103:92–96. <https://doi.org/10.1016/j.jhin.2019.06.006>

12. Ben-Ami R, Berman J, Novikov A, Bash E, Shachor-Meyouhas Y, Zakin S. 2017. Multidrug-resistant *Candida haemulonii* and *C. auris*, Tel Aviv, Israel. *Emerg Infect Dis* 23:195–203. <https://doi.org/10.3201/eid2302.161486>

13. Brown JL, Delaney C, Short B, Butcher MC, McCloud E, Williams C, Kean R, Ramage G. 2020. *Candida auris* phenotypic heterogeneity determines pathogenicity *in vitro*. *mSphere* 5:e00371-20. <https://doi.org/10.1128/mSphere.00371-20>

14. Wurster S, Bandi A, Beyda ND, Albert ND, Raman NM, Raad II, Kontoyiannis DP. 2019. *Drosophila melanogaster* as a model to study virulence and azole treatment of the emerging pathogen *Candida auris*. *J Antimicrob Chemother* 74:1904–1910. <https://doi.org/10.1093/jac/dkz100>

15. Borman AM, Szekely A, Johnson EM. 2016. Comparative pathogenicity of United Kingdom isolates of the emerging pathogen *Candida auris* and other key pathogenic *Candida* species. *mSphere* 1:e00189-16. <https://doi.org/10.1128/mSphere.00189-16>

16. Bing J, Guan Z, Zheng T, Ennis CL, Nobile CJ, Chen C, Chu H, Huang G. 2024. Rapid evolution of an adaptive multicellular morphology of *Candida auris* during systemic infection. *Nat Commun* 15:2381. <https://doi.org/10.1038/s41467-024-46786-8>

17. Balakumar A, Cox A, Thangamani S. 2024. Cell aggregation mediated by ACE2 deletion in *Candida auris* modulates fungal colonization and host immune responses in the skin. *mSphere* 9:e00734-24. <https://doi.org/10.1128/msphere.00734-24>

18. Ku TSN, Walraven CJ, Lee SA. 2018. *Candida auris*: disinfectants and implications for infection control. *Front Microbiol* 9:726. <https://doi.org/10.3389/fmicb.2018.00726>
19. Kean R, Sherry L, Townsend E, McCloud E, Short B, Akinbobola A, Mackay WG, Williams C, Jones BL, Ramage G. 2018. Surface disinfection challenges for *Candida auris*: an *in-vitro* study. *J Hosp Infect* 98:433–436. <https://doi.org/10.1016/j.jhin.2017.11.015>
20. Welsh RM, Bentz ML, Shams A, Houston H, Lyons A, Rose LJ, Litvintseva AP. 2017. Survival, persistence, and isolation of the emerging multidrug-resistant pathogenic yeast *Candida auris* on a plastic health care surface. *J Clin Microbiol* 55:2996–3005. <https://doi.org/10.1128/JCM.00921-17>
21. Kim HY PhD, Nguyen TA MSc, Kidd S PhD, Chambers J MD, Alastruey-Izquierdo A PhD, Shin J-H MD, Dao A PhD, Forastiero A MD, Wahyuning-sih R MD, Chakrabarti A MD, Beyer P, Gigante V PhD, Beardsley J PhD, Sati H PhD, Morrissey CO PhD, Alfenaar J-W PhD. 2024. *Candida auris*-a systematic review to the world health organization fungal priority pathogens list. *Med Mycol* 62:myae042. <https://doi.org/10.1093/mmy/myae042>
22. Kordalewska M, Lee A, Park S, Berrio I, Chowdhary A, Zhao Y, Perlin DS. 2018. Understanding echinocandin resistance in the emerging pathogen *Candida auris*. *Antimicrob Agents Chemother* 62:e00238-18. <https://doi.org/10.1128/AAC.00238-18>
23. Kordalewska M, Cancino-Prado G, Nobrega de Almeida Júnior J, Brasil Brandão I, Tigulini de Souza Peral R, Colombo AL, Perlin DS. 2023. Novel non-hot spot modification in Fks1 of *Candida auris* confers echinocandin resistance. *Antimicrob Agents Chemother* 67:e00423-23. <https://doi.org/10.1128/aac.00423-23>
24. Sharma D, Paul RA, Rudramurthy SM, Kashyap N, Bhattacharya S, Soman R, et al. 2022. Impact of FKS1 genotype on echinocandin *in vitro* susceptibility in *Candida auris* and *in vivo* response in a murine model of infection. *Antimicrob Agents Chemother* 66:e0165221. <https://doi.org/10.1128/AAC.01652-21>
25. Berman J, Krysan DJ. 2020. Drug resistance and tolerance in fungi. *Nat Rev Microbiol* 18:319–331. <https://doi.org/10.1038/s41579-019-0322-2>
26. Yang F, Scopel EFC, Li H, Sun L-L, Kwar N, Cao Y-B, Jiang Y-Y, Berman J. 2023. Antifungal tolerance and resistance emerge at distinct drug concentrations and rely upon different aneuploid chromosomes. *mBio* 14:e00227-23. <https://doi.org/10.1128/mbio.00227-23>
27. Rosenberg A, Ene IV, Bibi M, Zakin S, Segal ES, Ziv N, Dahan AM, Colombo AL, Bennett RJ, Berman J. 2018. Antifungal tolerance is a subpopulation effect distinct from resistance and is associated with persistent candidemia. *Nat Commun* 9:2470. <https://doi.org/10.1038/s41467-018-04926-x>
28. Todd RT, Soisangwan N, Peters S, Kemp B, Crooks T, Gerstein A, Selmecki A. 2023. Antifungal drug concentration impacts the spectrum of adaptive mutations in *Candida albicans*. *Mol Biol Evol* 40:msad009. <https://doi.org/10.1093/molbev/msad009>
29. Brauner A, Fridman O, Gefen O, Balaban NQ. 2016. Distinguishing between resistance, tolerance and persistence to antibiotic treatment. *Nat Rev Microbiol* 14:320–330. <https://doi.org/10.1038/nrmicro.2016.34>
30. Balázs D, Tóth Z, Locke JB, Borman AM, Forgács L, Balla N, Kovács F, Kovács R, Amano C, Baran TI, Majoros L. 2024. *In vivo* efficacy of rezafungin, anidulafungin, caspofungin, and micafungin against four *Candida auris* clades in a neutropenic mouse bloodstream infection model. *J Fungi (Basel)* 10:617. <https://doi.org/10.3390/jof10090617>
31. Yang F, Zhang L, Wakabayashi H, Myers J, Jiang Y, Cao Y, Jimenez-Ortigosa C, Perlin DS, Rustchenko E. 2017. Tolerance to caspofungin in *Candida albicans* is associated with at least three distinctive mechanisms that govern expression of *FKS* genes and cell wall remodeling. *Antimicrob Agents Chemother* 61:e00071-17. <https://doi.org/10.1128/AAC.00071-17>
32. Vande Zande P, Gautier C, Kwar N, Maufrais C, Metzner K, Wash E, Beach AK, Bracken R, Maciel EI, Pereira de Sá N, Fernandes CM, Solis NV, Del Poeta M, Filler SG, Berman J, Ene IV, Selmecki A. 2024. Step-wise evolution of azole resistance through copy number variation followed by KSR1 loss of heterozygosity in *Candida albicans*. *PLoS Pathog* 20:e1012497. <https://doi.org/10.1371/journal.ppat.1012497>
33. Gautier C, Maciel EI, Ene IV. 2024. Approaches for identifying and measuring heteroresistance in azole-susceptible *Candida* isolates. *Microbiol Spectr* 12:e04041-23. <https://doi.org/10.1128/spectrum.04041-23>
34. Sionov E, Lee H, Chang YC, Kwon-Chung KJ. 2010. *Cryptococcus neoformans* overcomes stress of azole drugs by formation of disomy in specific multiple chromosomes. *PLoS Pathog* 6:e1000848. <https://doi.org/10.1371/journal.ppat.1000848>
35. Sionov E, Chang YC, Kwon-Chung KJ. 2013. Azole heteroresistance in *Cryptococcus neoformans*: emergence of resistant clones with chromosomal disomy in the mouse brain during fluconazole treatment. *Antimicrob Agents Chemother* 57:5127–5130. <https://doi.org/10.1128/AAC.00694-13>
36. Ben-Ami R, Zimmerman O, Finn T, Amit S, Novikov A, Wertheimer N, Lurie-Weinberger M, Berman J. 2016. Heteroresistance to fluconazole is a continuously distributed phenotype among *Candida glabrata* clinical strains associated with *in vivo* Persistence. *mBio* 7:e00655-16. <https://doi.org/10.1128/mBio.00655-16>
37. Zhai B, Liao C, Jaggavarapu S, Tang Y, Rolling T, Ning Y, Sun T, Bergin SA, Gjonbalaj M, Miranda E, Babady NE, Bader O, Taur Y, Butler G, Zhang L, Xavier JB, Weiss DS, Hohl TM. 2024. Antifungal heteroresistance causes prophylaxis failure and facilitates breakthrough *Candida parapsilosis* infections. *Nat Med* 30:3163–3172. <https://doi.org/10.1038/s41591-024-03183-4>
38. Berman J. 2016. Ploidy plasticity: a rapid and reversible strategy for adaptation to stress. *FEMS Yeast Res* 16:fow020. <https://doi.org/10.1093/femsyr/fow020>
39. Lin S-Y, Huang H-Y, Chang L-L, Wang Y-L, Chen T-C, Chang K, Tu H-P, Lu P-L. 2024. The impact of the fluconazole trailing effect on the persistence of *Candida albicans* bloodstream infection when treated with fluconazole. *Clin Microbiol Infect* 30:945–950. <https://doi.org/10.1016/j.cmi.2024.03.023>
40. Kim SH, Iyer KR, Pardeshi L, Muñoz JF, Robbins N, Cuomo CA, Wong KH, Cowen LE. 2019. Erratum for Kim et al., “genetic analysis of *Candida auris* implicates Hsp90 in morphogenesis and azole tolerance and Cdr1 in azole resistance”. *mBio* 10:e00346-19. <https://doi.org/10.1128/mBio.00346-19>
41. Healey KR, Nagasaki Y, Zimmerman M, Kordalewska M, Park S, Zhao Y, Perlin DS. 2017. The gastrointestinal tract is a major source of echinocandin drug resistance in a murine model of *Candida glabrata* colonization and systemic dissemination. *Antimicrob Agents Chemother* 61:e01412-17. <https://doi.org/10.1128/AAC.01412-17>
42. Arastehfar A, Daneshnia F, Cabrera N, Penalva-Lopez S, Sarathy J, Zimmerman M, Shor E, Perlin DS. 2023. Macrophage internalization creates a multidrug-tolerant fungal persister reservoir and facilitates the emergence of drug resistance. *Nat Commun* 14:1183. <https://doi.org/10.1038/s41467-023-36882-6>
43. Rasouli Koohi S, Shankararayan SA, Galon CM, Charlebois DA. 2023. Identification and elimination of antifungal tolerance in *Candida auris* *Biomedicines* 11:898. <https://doi.org/10.3390/biomedicines11030898>
44. Sarfatis A, Wang Y, Twumasi-Ankrah N, Moffitt JR. 2025. Highly multiplexed spatial transcriptomics in bacteria. *Science* 387:eadr0932. <https://doi.org/10.1126/science.adr0932>
45. Roberts JA, Sime FB, Lipman J, Hernández-Mitre MP, Baptista JP, Brüggemann RJ, Darvall J, De Waele JJ, Dimopoulos G, Lefrant J-Y, Mat Nor MB, Rello J, Seoane L, Slavina MA, Valkonen M, Venditti M, Ceccarelli G, Wong WT, Zeitlinger M, Roger C. 2025. Are contemporary antifungal doses sufficient for critically ill patients? outcomes from an international, multicenter pharmacokinetics study for screening antifungal exposure in intensive care units—the SAFE-ICU study. *Intensive Care Med* 51:302–317. <https://doi.org/10.1007/s00134-025-07793-5>
46. Zhang M, Zhao Y, Cui H, Huang W, Xiong K, Yang S, Duan Y, He Y, Yang L, Su C, Lu Y. 2025. CO₂ potentiates echinocandin efficacy during invasive candidiasis therapy via dephosphorylation of Hsp90 by Ptc2 in condensates. *Proc Natl Acad Sci U S A* 122:e2417721122. <https://doi.org/10.1073/pnas.2417721122>
47. Lamoth F, Lewis RE, Kontoyiannis DP. 2020. Role and interpretation of antifungal susceptibility testing for the management of invasive fungal infections. *J Fungi (Basel)* 7:17. <https://doi.org/10.3390/jof7010017>
48. Theuretzbacher U. 2012. Pharmacokinetic and pharmacodynamic issues for antimicrobial therapy in patients with cancer. *Clin Infect Dis* 54:1785–1792. <https://doi.org/10.1093/cid/cis210>
49. Ribeiro F de C, Kemmerich KK, Gonçalves JC, Junqueira JC, Mannan M, Nabeela S, Colombo AL, Uppuluri P. 2024. *Candida albicans* recovered from persistent candidemia exhibit enhanced virulence traits. *J Infect Dis* 312:1093. <https://doi.org/10.1093/infdis/jiae631>