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Rezafungin: an opportunity to personalize the treatment of patients with candidemia

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We appreciate the thoughtful commentary by Wang et al. and welcome the opportunity to further elaborate on the key aspects related to the use of rezafungin in critically ill patients by replying to his letter.

While this letter and the work entitled "The personalized treatment of invasive candidiasis still has a long way to go" [1] are surely commendable, several points merit further discussion. The authors raised some questions regarding our sub-analyses of rezafungin use in the intensive care unit (ICU) [2, 3]. We would like to provide answers by the following additional information:

Question 1: While the once-weekly administration significantly improves patient compliance, the pathophysiological status of critically ill patients, particularly liver function, can change rapidly. Whether therapeutic drug monitoring (TDM) is required during treatment and whether it is unnecessary to adjust the drug dosage based on liver function still need further investigation.

Answer to question 1: We would like to mention that classical echinocandins have been associated with low serum concentrations in critically ill patients leading to sub-optimal PKPD target achievement (area under the curve [AUC]/minimal inhibitory concentration [MIC]) [4, 5]. In contrast, population pharmacokinetic (PK) modeling of rezafungin using data from phase 1, 2, and 3 studies showed that no clinical meaningful PK variation was observed along co-variates including body mass index, albumin, or diseases state comprising liver diseases [6]. In addition, a recent literature review has shown that rezafungin appears to be suitable for use in a variety of special populations without the need for dose modifications based on available data, including patients with organ dysfunction or obesity, and elderly and critically ill patients [7].

Deterioration of liver function may occur in ICU patients. It is unlikely though that rezafungin adds to such development. In a phase 2 double-blind randomized clinical trial, patients with candidemia and/or invasive candidiasis were treated with either once-weekly rezafungin or intravenous caspofungin, no notable differences were found in treatment-emergent hepatic adverse events across the different study groups (rezafungin

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400 mg/400 mg, rezafungin 400 mg/200 mg, and caspofungin at licensed dosing) [8]. Indeed, in the rezafungin 400 mg/200 mg group there was a lower incidence of treatment-emergent adverse events leading to study drug discontinuation and of serious adverse events leading to death [8]. In a phase 3 double-blind randomized controlled trial comparing rezafungin 400/200 with caspofungin at licensed dosing, hepatic adverse events were rare [9]. However, classical adverse events related with echinocandins like hypokalemia, and gastrointestinal adverse events (diarrhea and vomiting) were also common with rezafungin and should be monitored.

Question 2: Patients with candidemia who are in shock still require hospitalization, even in the ICU. How to accurately select the antifungal drugs based on susceptibility breakpoints, whether repeat blood cultures are necessary, and whether the time to negativity in blood cultures has clinical significance if individualized treatment is not feasible remain questions.

Answer to question 2: As per current guidelines, repeat blood cultures are necessary to determine the overall duration of treatment, i.e. blood culture negativity plus 14 days. Whether time to blood culture negativity is clinically relevant remains to be determined. Shorter duration of blood stream infection should translate into less complication. The shorter time to negative blood cultures found with rezafungin would have facilitated earlier discharge in 16% of patients [8, 9]. Interestingly, the Candida III study found the same effect size [10].

Question 3: Is it necessary to routinely test for rezafungin susceptibility? When the treatment outcome is unsatisfactory, should FKS mutations be screened? These questions require guidance from professors specializing in pharmacy.

Answer to question 3: Given the broad susceptibility of *Candida* spp to echinocandins, antifungal susceptibility testing is not routinely performed in all centers managing candidemia. Rezafungin is structurally related to anidulafungin, and current in vitro data support inferring susceptibility to rezafungin from susceptibility to anidulafungin [11].

We acknowledge the growing concern regarding emerging echinocandin resistance and agree that close surveillance of resistance trends is essential. A most concerning situation is intrabdominal candidiasis [12], probably due to the lower exposure to echinocandins in peritoneal fluid [13]. In a murine model rezafungin exhibited higher diffusion to intrabdominal abscesses as compared to micafungin [14]. More clinical experience is needed to confirm this potential advantage in humans.

Question 4: Is it necessary to further consider the cost implications from a health economics perspective?

Answer to question 4: We agree with the authors that health resources are limited, and it is necessary to select those patients who benefit from an antifungal showing better PK properties and demonstrating shorter time to negative blood cultures. We suggest that those with non-catheter related candidemia, presenting with sepsis or septic shock are the best candidates since the probability to achieve the PK/PD target is higher with the standard dose of rezafungin than with other echinocandins, even more so in critically ill patients with hypoalbuminemia and obesity. Although there was no difference in mortality, it is also true that the mortality in rezafungin clinical trials was around 20%. That is the baseline mortality in patients with similar characteristics but without candidemia [15].

Perspectives in health economics must be differentiated and the mere drug acquisition costs is only one factor in a payer perspective health economics appraisal [16]. To shorten the hospital length of stay, reduces the risk of complications related with IV lines, the acquisition of nosocomial infections, particularly those caused by multidrug resistant pathogens, increases the number of available beds for other patients, and alleviates the patient and his/her families' suffering. Rezafungin, as the first long-acting antifungal agent with minimal drug-drug interactions, represents an excellent opportunity to reduce the length of hospital stay of those patients requiring prolong use of antifungals, for example patients with endocarditis or bone and joint infections [3, 17].

In conclusion:

We appreciate the thoughtful commentary by Wang and colleagues and welcome the opportunity to further elaborate on the key aspects related to the use of rezafungin in critically ill patients. While acknowledging the challenges that remain in the personalized treatment of invasive candidiasis, we believe that current evidence supports the role of rezafungin as a promising antifungal agent, particularly in complex ICU populations. The high loading dose (400 mg), and its higher water stability (leading to a prolong half-life), increase the total exposure during the first hours of candidemia. It may explain the shorter duration of candidemia in comparison to caspofungin. In addition, its favorable safety profile, and once-weekly dosing regimen offer potential clinical advantages including earlier discharge. Nonetheless, we agree that continuous monitoring of resistance trends, further clinical experience, and health-economic assessments are essential to optimize its use and better define the populations who may derive the most benefit. We hope that our additional clarifications contribute to the ongoing discussion on the evolving management of candidemia.

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PMH, OAC & AS. designed the paper. PMH, OAC & AS participated in drafting and reviewing. PMH, OAC & AS read and approved the final version of the manuscript.

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Declarations

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Not applicable.

Consent for publication
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References

1. Wang L, Xu C, Chen Y, Zhou M, Li R, Lin B, Yu Y. The personalized treatment of invasive candidiasis still has a long way to go. Crit Care. 2025;29(1):197. https://doi.org/10.1186/s13054-025-05444-1. PMID: 40390060; PMCID: PMC12087206.
2. Honoré PM, Girardis M, Kollef M, Cornely OA, Thompson GR 3rd, Bassetti M, et al. Rezafungin versus Caspofungin for patients with candidaemia or invasive candidiasis in the intensive care unit: pooled analyses of the restore and STRIVE randomised trials. Crit Care. 2024;28(1):348.
3. Honoré PM, Bassetti M, Cornely OA, Dupont H, Fortún J, Kollef MH, et al. Length of hospital and intensive care unit stay in patients with invasive candidiasis and/or candidemia treated with rezafungin: a pooled analysis of two randomised controlled trials. Crit Care. 2024;28(1):361.
4. Elkayal O, Hoffert Y, Mertens B, Van Daele R, Lagrou K, Wauters J et al. Anidulafungin exposure and population pharmacokinetics in critically ill patients with invasive candidiasis. Infection. 2024. https://doi.org/10.1007/s15010-024-02448-x. Epub ahead of print. PMID: 39641856.
5. Roberts JA, Sime FB, Lipman J, Hernández-Mitre MP, Baptista JP, Brüggemann RJ, et al. 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. 2025;51(2):302–17. Epub 2025 Feb 3. PMID: 39899034; PMCID: PMC11903579.
6. Roepcke S, Passarell J, Walker H, Flanagan S. Population Pharmacokinetic modeling and target attainment analyses of Rezafungin for the treatment of candidemia and invasive candidiasis. Antimicrob Agents Chemother. 2023;67(12):e0091623. https://doi.org/10.1128/aac.00916-23. Epub 2023 Nov 28. PMID: 38014945; PMCID: PMC10720538.
7. Cornely OA, Dupont H, Mikulska M, Rautemaa-Richardson R, Garcia-Vidal C, Thompson GR 3 et al. rdRezafungin in special populations with candidaemia and/or invasive candidiasis. J Infect. 2025;90(3):106435. https://doi.org/10.1016/j.jinf.2025.106435. Epub 2025. PMID: 39921063.
8. Thompson GR, Soriano A, Skoutelis A, Vazquez JA, Honore PM, Horcajada JP, et al. Rezafungin versus Caspofungin in a phase 2, randomized, double-blind study for the treatment of candidemia and invasive candidiasis: the STRIVE trial. Clin Infect Dis. 2021;73(11):e3647–55.
9. Thompson GR 3rd, Soriano A, Cornely OA, Kullberg BJ, Kollef M, Vazquez J, et al. Rezafungin versus Caspofungin for treatment of candidaemia and invasive candidiasis (ReSTORE): a multicentre, double-blind, double-dummy, randomised phase 3 trial. Lancet. 2023;401(10370):49–59.
10. Hoenigl M, Salmanton-García J, Egger M, ECMM Candida III Study Group, et al. Guideline adherence and survival of patients with candidaemia in europe: results from the ECMM Candida III multinational European observational cohort study. Lancet Infect Dis. 2023;23(6):751–61. https://doi.org/10.1016/S1473-3099(22)00872-6. Epub 2023 Feb 15. PMID: 37254300.
11. Ceballos-Garzon A, Holzapfel M, Welsch J, Mercer D. Identification and antifungal susceptibility patterns of reference yeast strains to novel and conventional agents: a comparative study using CLSI, EUCAST and sensititre YeastOne methods. JAC Antimicrob Resist. 2025;7(2):dlaf040. https://doi.org/10.1093/jacamr/dlaf040. PMID: 40110552; PMCID: PMC11920621.
12. Díaz-García J, Machado M, Alcalá L et al. CANDIMAD study group. Antifungal resistance in Candida spp within the intra-abdominal cavity: study of resistance acquisition in patients with serial isolates. Clin Microbiol Infect. 2023;29(12):1604.e1-1604.e6. doi: 10.1016/j.cmi.2023.08.021. Epub 2023. PMID: 37640239.
13. Gioia F, Gomez-Lopez A, Alvarez ME, et al. Pharmacokinetics of echinocandins in suspected candida peritonitis: A potential risk for resistance. Int J Infect Dis. 2020;101:24–8. https://doi.org/10.1016/j.ijid.2020.09.019. Epub 2020 Sep 13. PMID: 32937195.
14. Zhao Y, Prideaux B, Nagasaki Y, Lee MH, Chen PY, Blanc L, et al. Unraveling drug penetration of Echinocandin antifungals at the site of infection in an Intra-abdominal abscess model. Antimicrob Agents Chemother. 2017;61(10):e01009–17. https://doi.org/10.1128/AAC.01009-17. PMID: 28739797; PMCID: PMC5610477.
15. Salmanton-García J, Cornely OA, Stemler J, Barać A, Steinmann J, Siváková A, Akalin EH, et al. Attributable mortality of candidemia - Results from the ECMM Candida III multinational European observational cohort study. J Infect. 2024;89(3):106229. Epub 2024 Jul 16. PMID: 39025408.
16. Jeck J, Jakobs F, Kurte MS, Cornely OA, Kron F. Health-economic modelling of cost savings due to the use of Rezafungin based on a German cost-of-illness study of candidiasis. JAC Antimicrob Resist. 2023;5(3):dlad079. https://doi.org/10.1093/jacamr/dlad079. PMID: 37342199; PMCID: PMC10279419.
17. Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, Mycoses Study Group. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. Clin Infect Dis. 2012;54(8):1110-22. https://doi.org/10.1093/cid/cis021.

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