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Published in:
Antimicrobial Agents and Chemotherapy

DOI:
10.1128/AAC.00465-21

Publication date:
2021

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

AUTHOR REPLY

Reply to Van Daele et al., "Fluconazole Underexposure in Critically Ill Patients: a Matter of Using the Right Targets?"

A.-G. Märtson,[a] J. M. Boonstra,[a] I. Sandaradura,[b,c] J. G. W. Kosterink,[a,d] T. S. van der Werf,[e,f] D. J. E. Marriott,[g,h] J. G. Zijlstra,[i] D. J. Touw,[a] J. W. C. Alffenaar[b,c,j]

[a]University of Groningen, University Medical Center Groningen, Department of Clinical Pharmacy and Pharmacology, Groningen, the Netherlands
[b]The University of Sydney, Faculty of Medicine and Health, School of Pharmacy, Sydney, Australia
[c]Westmead Hospital, Sydney, Australia
[d]University of Groningen, Department of Pharmacy, Section of Pharmacotherapy and Pharmaceutical Care, Groningen, the Netherlands
[e]University of Groningen, University Medical Center Groningen, Department of Internal Medicine, Groningen, the Netherlands
[f]University of Groningen, University Medical Center Groningen, Department of Pulmonary Diseases and Tuberculosis, Groningen, the Netherlands
[g]St. Vincent's Clinical School, University of New South Wales, Kensington, NSW, Australia
[h]Department of Clinical Microbiology and Infectious Diseases, St. Vincent's Hospital, Darlinghurst, NSW, Australia
[i]University of Groningen, University Medical Center Groningen, Department of Critical Care, Groningen, the Netherlands
[j]Marie Bashir Institute of Infectious Diseases and Biosecurity, University of Sydney, Sydney, Australia

A.-G. Märtson and J. M. Boonstra contributed equally. Author order was determined by seniority.

We thank Van Daele et al. (1) for their interest in our study investigating pharmacokinetics in critically ill patients with the aim of optimizing fluconazole dosing for the prevention and treatment of invasive candida infections (2). We welcome the comments on our ideas about the right dose to achieve the *f*AUC/MIC exceeding 100 in most patients.

Van Daele et al. mention that based on the well-accepted target *f*AUC/MIC of 100 and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) cutoff of 2 mg/liter, the target exposure should be 200 mg · h/liter instead of 400 mg · h/liter. By using a lower exposure target, the current recommended dosing regimen of 800 mg for the oral loading dose (~12 mg/kg of body weight) followed by a 400-mg maintenance dose (~6 mg/kg) once daily would not require dose escalation, which would potentially reduce the risk of adverse drug effects.

In our approach, we used the EUCAST MIC of ≥4 mg/liter, which is defined as fluconazole resistance for most *Candida* species. To avoid confusion, EUCAST does not include the intermediate category in their tables (3). Organisms falling into this category are classified by EUCAST as "susceptible increased exposure," signifying that the pathogen can be considered susceptible if treated with a higher dose. When fluconazole is initiated for the prevention and treatment of *Candida* infections, the MIC is often not known, so we aimed to ensure that modified dosing regimens covered the intermediate category. In critically ill patients, early initiation of adequate treatment is key. Moreover, in the case of deep-seated infections, the concentration at the site of infection may be lower, potentially resulting in a suboptimal treatment response.

In the study by Muilwijk et al., an approach comparable to ours was used by targeting an MIC of ≤4 mg/liter (4). In their study, a maintenance dose of 400 to 800 mg once daily based on renal function was required to achieve a satisfactory target attainment.

We agree with Van Daele et al. that a personalized approach would be ideal, including a dose selection solely on patient characteristics, anticipating a susceptible pathogen (MIC ≤ 2 mg/liter), thereby avoiding the need for therapeutic drug monitoring (TDM). It would indeed result in early target attainment (5). However, it may be oversimplifying critical care medicine. The pharmacokinetics in critically ill patients are not predictable and stable during their stay in the intensive care unit (ICU), as there are many pathophysiological changes as

Citation Märtson A-G, Boonstra JM, Sandaradura I, Kosterink JGW, van der Werf TS, Marriott DJE, Zijlstra JG, Touw DJ, Alffenaar JWC. 2021. Reply to Van Daele et al., "Fluconazole underexposure in critically ill patients: a matter of using the right targets?" Antimicrob Agents Chemother 65:e00465-21. https://doi.org/10.1128/AAC.00465-21.

Address correspondence to J. W. C. Alffenaar, johannes.alffenaar@sydney.edu.au.

This is a response to a letter by Van Daele et al. https://doi.org/10.1128/AAC.00430-21.

Accepted manuscript posted online 29 March 2021

Published 18 May 2021

well as external factors, such as renal replacement therapy, resulting in variation in the patient condition over time, thereby influencing drug exposure. The introduction of liquid chromatography-tandem mass spectrometry (LC-MS/MS) in clinical laboratories has enabled short turnaround times to support TDM in critically ill patients (6). We do agree with Van Daele et al. that, unfortunately, this service is not frequently offered (7). This service is considered expensive and complex, as it requires highly skilled analytical scientists and clinical pharmacologists interpreting the drug concentrations and performing model-informed precision dosing (7, 8). However, with an increasing body of evidence to support TDM in critically ill patients, now is the time to take action. Data from cost-effectiveness studies will be very important to convince a hospital administration to invest in an adequate TDM service to optimize treatment in critically ill patients.

ACKNOWLEDGMENT

A.-G.M. was funded by Marie Skłodowska-Curie Actions (grant agreement no. 713660–PRONKJEWAIL–H2020-MSCA-COFUND-2015). None of the financial support is related to this article.

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