AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

Efficient Recovery of *Candida auris* and Five Other Medically Important *Candida* Species from Blood Cultures Containing Clinically Relevant Concentrations of Antifungal Agents

Brunella Posteraro, Giulia Menchinelli, Vittorio Ivagnes, Venere Cortazzo, Flora Liotti, Benedetta Falasca, Barbara Fiori, Tiziana D'Inzeo, Teresa Spanu, Giulia De Angelis, and Maurizio Sanguinetti

Corresponding Author(s): Maurizio Sanguinetti, Fondazione Policlinico Universitario Agostino Gemelli IRCCS

Review Timeline:

Submission Date:	October 8, 2022
Editorial Decision:	December 4, 2022
Revision Received:	January 2, 2023
Accepted:	January 9, 2023

Editor: Alexandre Alanio

Reviewer(s): The reviewers have opted to remain anonymous.

Transaction Report:

(Note: With the exception of the correction of typographical or spelling errors that could be a source of ambiguity, letters and reports are not edited. The original formatting of letters and referee reports may not be reflected in this compilation.)

DOI: https://doi.org/10.1128/spectrum.04104-22

December 4, 2022

Prof. Maurizio Sanguinetti
Fondazione Policlinico Universitario
Microbiology
L.go A. Gemelli 8
Rome, RM 168
Italy

Re: Spectrum04104-22 (Efficient Recovery of *Candida auris* and Five Other Medically Important *Candida* Species from Blood Cultures Containing Clinically Relevant Concentrations of Antifungal Agents)

Dear Prof. Maurizio Sanguinetti:

Both reviewers found the study well executed and useful for our community.
They both pointed out that Biomerieux was involved in reviewing the manuscript. The authors should precise if the results were amended or modified after these reviewing or if it was only minor modifications. Please explain in detais.

Thank you for submitting your manuscript to Microbiology Spectrum. When submitting the revised version of your paper, please provide (1) point-by-point responses to the issues raised by the reviewers as file type "Response to Reviewers," not in your cover letter, and (2) a PDF file that indicates the changes from the original submission (by highlighting or underlining the changes) as file type "Marked Up Manuscript - For Review Only". Please use this link to submit your revised manuscript - we strongly recommend that you submit your paper within the next 60 days or reach out to me. Detailed instructions on submitting your revised paper are below.

Link Not Available

Below you will find instructions from the Microbiology Spectrum editorial office and comments generated during the review.

ASM policy requires that data be available to the public upon online posting of the article, so please verify all links to sequence records, if present, and make sure that each number retrieves the full record of the data. If a new accession number is not linked or a link is broken, provide production staff with the correct URL for the record. If the accession numbers for new data are not publicly accessible before the expected online posting of the article, publication of your article may be delayed; please contact the ASM production staff immediately with the expected release date.

The ASM Journals program strives for constant improvement in our submission and publication process. Please tell us how we can improve your experience by taking this quick Author Survey.

Sincerely,

Alexandre Alanio

Editor, Microbiology Spectrum

Journals Department
American Society for Microbiology
1752 N St., NW
Washington, DC 20036
E-mail: spectrum@asmusa.org

Reviewer comments:

Reviewer #2 (Comments for the Author):

The authors have investigated the efficiency of different blood culture media of the automated blood culture systems containing clinically relevant concentrations of antifungal drugs in isolation of six Candida species, including Candida auris. A clinical blood culture simulation model was used. Ultimately, the effect of the neutralizing resins on the existing antifungal drug was explored and differential data for different classes of antifungal drugs and varying Candida species were obtained. The presented data

are useful for daily medical practice, given the high number of patients receiving antifungal drugs and requiring blood culturing per their clinical manifestations. Some comments and inquiries:
1. Lines 112-116. The main conclusion of the study is that the neutralizing resins used may not be adequate for echinocandins but appear to neutralize the effect of azoles and amphotericin B in general. May the authors comment on this "further", considering the chemical structure of echinocandins?
2. Similary, regarding the varying effects on different species of Candida - -What are the possible factors that may have influence on this? (growth rate, etc...) Adding an additional short discussion may be helpful.
3. Line 158. "Slightly", "moderately", or "highly delayed": Please insert exact definitions and relevant references at this point.
4. Lines 277-278. CDC tentative C. auris breakpoints should also be referenced and acknowledged at this point.

Reviewer #3 (Comments for the Author):

This is an interesting and well-executed study which provides valuable information on the reliability of blood culture in the presence of various antifungals. The authors are to be congratulated on the thoroughness of their methods.

I have a few small suggestions that I feel would be beneficial for the manuscript.

Candida glabrata and *Candida krusei* have relatively recently had name changes which are increasingly being used. Whilst I understand for familiarity the authors may choose to continue using their older names, I feel it would be helpful to also mention their newer names: *Nakaseomyces glabrata* and *Pichia kudriavzevii* respectively.

P5 - L87-91. It would make the reading of the manuscript slightly easier if the authors included the range of antifungal concentrations used as 100%, 50% and 25% PSL in the main body of the text as well as in the supplementary information.

Staff Comments:

Preparing Revision Guidelines
To submit your modified manuscript, log onto the eJP submission site at https://spectrum.msubmit.net/cgi-bin/main.plex. Go to Author Tasks and click the appropriate manuscript title to begin the revision process. The information that you entered when you first submitted the paper will be displayed. Please update the information as necessary. Here are a few examples of required updates that authors must address:

• Point-by-point responses to the issues raised by the reviewers in a file named "Response to Reviewers," NOT IN YOUR COVER LETTER.
• Upload a compare copy of the manuscript (without figures) as a "Marked-Up Manuscript" file.
• Each figure must be uploaded as a separate file, and any multipanel figures must be assembled into one file.
• Manuscript: A .DOC version of the revised manuscript
• Figures: Editable, high-resolution, individual figure files are required at revision, TIFF or EPS files are preferred

For complete guidelines on revision requirements, please see the journal Submission and Review Process requirements at https://journals.asm.org/journal/Spectrum/submission-review-process. **Submissions of a paper that does not conform to Microbiology Spectrum guidelines will delay acceptance of your manuscript.** "

Please return the manuscript within 60 days; if you cannot complete the modification within this time period, please contact me. If you do not wish to modify the manuscript and prefer to submit it to another journal, please notify me of your decision immediately so that the manuscript may be formally withdrawn from consideration by Microbiology Spectrum.

If your manuscript is accepted for publication, you will be contacted separately about payment when the proofs are issued; please follow the instructions in that e-mail. Arrangements for payment must be made before your article is published. For a complete list of **Publication Fees**, including supplemental material costs, please visit our[website](website).

Corresponding authors may join or renew ASM membership to obtain discounts on publication fees. Need to upgrade your membership level? Please contact Customer Service at Service@asmusa.org.

Thank you for submitting your paper to Microbiology Spectrum.

Re: Spectrum04104-22 (Efficient Recovery of Candida auris and Five Other Medically Important Candida Species from Blood Cultures Containing Clinically Relevant Concentrations of Antifungal Agents)

Editor (Comment for the Author):
Both reviewers found the study well executed and useful for our community.
They both pointed out that bioMérieux was involved in reviewing the manuscript. The authors should precise if the results were amended or modified after these reviewing or if it was only minor modifications. Please explain in detail.
Answer: I have added a specification of how bioMérieux reviewed the manuscript via a short sentence in the Acknowledgments section. See page 15, lines 342 to 344 of the revised manuscript.

Reviewer #2 (Comments for the Author):
The authors have investigated the efficiency of different blood culture media of the automated blood culture systems containing clinically relevant concentrations of antifungal drugs in isolation of six Candida species, including Candida auris. A clinical blood culture simulation model was used. Ultimately, the effect of the neutralizing resins on the existing antifungal drug was explored and differential data for different classes of antifungal drugs and varying Candida species were obtained. The presented data are useful for daily medical practice, given the high number of patients receiving antifungal drugs and requiring blood culturing per their clinical manifestations. Some comments and inquiries:
Answer: While I am very grateful to the reviewer for appreciating the manuscript, I have tried to substantiate my responses to the comments/questions raised by the reviewer. This implied the addition of two references (nos. 22 and 23).
1. Lines 112-116. The main conclusion of the study is that the neutralizing resins used may not be adequate for echinocandins but appear to neutralize the effect of azoles and amphotericin B in general. May the authors comment on this "further", considering the chemical structure of echinocandins?
Answer: As suggested by the reviewer, I have added a few sentences to "further" comment on the main conclusion of the study, discussing how the chemical structure of the echinocandins may have affected the main findings of the study. See page 10, lines 213 to 220, with enclosed reference no. 22, of the revised manuscript.
2. Similarly, regarding the varying effects on different species of Candida - -What are the possible factors that may have influence on this? (Growth rate, etc...) Adding an additional short discussion may be helpful.
Answer: As in the previous comment, I elaborated on factors that may have affected the apparent species-specificity of the study findings. See page 10, lines 220 to 223, with enclosed reference no. 23, of the revised manuscript.
3. Line 158. "Slightly", "moderately", or "highly delayed": Please insert exact definitions and relevant references at this point.
Answer: As suggested by the reviewer, I have added details about how the categories were established by us. See page 8, lines 157 to 159, and page 14, lines 325 to 329 of the revised manuscript.
4. Lines 277-278. CDC tentative C. auris breakpoints should also be referenced and acknowledged at this point.
Answer: As suggested by the reviewer, I have added a few sentences (with enclosed reference) to acknowledge the CDC tentative C. auris breakpoints. See page 13, lines 287 to 294 of the revised manuscript.

Reviewer #3 (Comments for the Author):

This is an interesting and well-executed study which provides valuable information on the reliability of blood culture in the presence of various antifungals. The authors are to be congratulated on the thoroughness of their methods. I have a few small suggestions that I feel would be beneficial for the manuscript.

Answer: While I am very grateful to the reviewer for appreciating the manuscript, I have tried to substantiate my responses to the suggestions raised by the reviewer.

Candida glabrata and Candida krusei have relatively recently had name changes which are increasingly being used. Whilst I understand for familiarity the authors may choose to continue using their older names, I feel it would be helpful to also mention their newer names: Nakaseomyces glabrata and Pichia kudriavzevii respectively.

Answer: As suggested by the reviewer, I have mentioned the newer names of Candida glabrata and Candida krusei. See page 4, lines 55 to 56 of the revised manuscript.

P5 - L87-91. It would make the reading of the manuscript slightly easier if the authors included the range of antifungal concentrations used as 100%, 50% and 25% PSL in the main body of the text as well as in the supplementary information.

Answer: As suggested by the reviewer, I have added in the main text (as already reported in Table S1) the antifungal concentrations used as 100%, 50%, and 25% PSL, respectively. See page 5, lines 86 to 89 of the revised manuscript.

January 9, 2023

Prof. Maurizio Sanguinetti
Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Microbiology
L.go A. Gemelli 8
Rome, RM 168
Italy

Re: Spectrum04104-22R1 (Efficient Recovery of *Candida auris* and Five Other Medically Important *Candida* Species from Blood Cultures Containing Clinically Relevant Concentrations of Antifungal Agents)

Dear Prof. Maurizio Sanguinetti:

Thank you for replying appropriately to reviewer's comments.

Your manuscript has been accepted, and I am forwarding it to the ASM Journals Department for publication. You will be notified when your proofs are ready to be viewed.

The ASM Journals program strives for constant improvement in our submission and publication process. Please tell us how we can improve your experience by taking this quick Author Survey.

Publication Fees: We have partnered with Copyright Clearance Center to collect author charges. You will soon receive a message from no-reply@copyright.com with further instructions. For questions related to paying charges through RightsLink, please contact Copyright Clearance Center by email at ASM_Support@copyright.com or toll free at +1.877.622.5543. Hours of operation: 24 hours per day, 7 days per week. Copyright Clearance Center makes every attempt to respond to all emails within 24 hours. For a complete list of **Publication Fees**, including supplemental material costs, please visit ourwebsite.

ASM policy requires that data be available to the public upon online posting of the article, so please verify all links to sequence records, if present, and make sure that each number retrieves the full record of the data. If a new accession number is not linked or a link is broken, provide production staff with the correct URL for the record. If the accession numbers for new data are not publicly accessible before the expected online posting of the article, publication of your article may be delayed; please contact the ASM production staff immediately with the expected release date.

Corresponding authors may join or renew ASM membership to obtain discounts on publication fees. Need to upgrade your membership level? Please contact Customer Service at Service@asmusa.org.

Thank you for submitting your paper to Spectrum.

Sincerely,

Alexandre Alanio
Editor, Microbiology Spectrum

Journals Department
American Society for Microbiology
1752 N St., NW
Washington, DC 20036
E-mail: spectrum@asmusa.org