although there was likely some difference in the sensitivity for isoniazid between what was reported by Manson et al and by Desjardin et al, the 95% CI for this parameter was 7%–38%. In other words, we would consider the magnitude and therefore the practical significance of this difference to be highly uncertain.

In conclusion, we share the authors' sentiment that the performance of genotypic drug-susceptibility assays can differ between settings because of the MTBC diversity [6]. This means that genotypic assays can miss a large proportion of resistant isolates or cause harm to patients due to systematic false-resistant results [7, 8]. Regular monitoring of routine diagnostic results and well-designed studies are therefore needed. Importantly, such studies should comprise detailed discrepancy analyses, including resequencing, ideally from the drug-containing medium, and repeat phenotypic testing to ensure that discrepancies are reproducible [9, 10].

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. C. U. K. is a consultant for the Foundation for Innovative New Diagnostics. The Bill & Melinda Gates Foundation and Janssen Pharmaceutica covered C. U. K.'s travel and accommodation to present at meetings. The European Society of Mycobacteriology awarded C. U. K. the Gertrud Meissner Award, which is sponsored by Hain Lifescience. C. U. K. has collaborated with Illumina Inc. on a number of scientific projects. D. L. D. is a consultant for the Foundation for Innovative New Diagnostics, GenoScreen, bigtech Labs, Genedrive Plc., and QuantuMDx Group Ltd. The remaining author has no reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Claudio U. Köser,[1] Leonardo A. Koeser,[2] and David L. Dolinger[3]

[1]Department of Genetics, University of Cambridge and [2]King's Health Economics, Department of Health Services and Population Research, Institute of Psychiatry, Psychology and Neuroscience, King's College London, United Kingdom; and [3]Medway, Massachusetts

References

1. Manson AL, Abeel T, Galagan JE, et al. *Mycobacterium tuberculosis* whole genome sequences from southern India suggest novel resistance mechanisms and the need for region-specific diagnostics. Clin Infect Dis **2017**; 64:1494–501.
2. Unissa AN, Selvakumar N, Narayanan S, Suganthi C, Hanna LE. Investigation of Ser315 substitutions within *katG* gene in isoniazid-resistant clinical isolates of *Mycobacterium tuberculosis* from south India. Biomed Res Int **2015**; 2015:257983.
3. Walker TM, Kohl TA, Omar SV, et al; Modernizing Medical Microbiology Informatics Group. Whole-genome sequencing for prediction of *Mycobacterium tuberculosis* drug susceptibility and resistance: a retrospective cohort study. Lancet Infect Dis **2015**; 15:1193–202.
4. Desjardins CA, Cohen KA, Munsamy V, et al. Genomic and functional analyses of *Mycobacterium tuberculosis* strains implicate ald in D-cycloserine resistance. Nat Genet **2016**; 48:544–51.
5. Gelman A, Carlin J. Beyond power calculations: assessing type S (sign) and type M (magnitude) errors. Perspect Psychol Sci **2014**; 9:641–51.
6. Köser CU, Feuerriegel S, Summers DK, Archer JA, Niemann S. Importance of the genetic diversity within the *Mycobacterium tuberculosis* complex for the development of novel antibiotics and diagnostic tests of drug resistance. Antimicrob Agents Chemother **2012**; 56:6080–7.
7. Sanchez-Padilla E, Merker M, Beckert P, et al. Detection of drug-resistant tuberculosis by Xpert MTB/RIF in Swaziland. N Engl J Med **2015**; 372:1181–2.
8. Ajileye A, Alvarez N, Merker M, et al. Some synonymous and nonsynonymous *gyrA* mutations in *Mycobacterium tuberculosis* lead to systematic false-positive fluoroquinolone resistance results with the Hain GenoType MTBDR*sl* assays. Antimicrob Agents Chemother **2017**; 61:e02169–16.
9. Zhang X, Liu L, Zhang Y, Dai G, Huang H, Jin Q. Genetic determinants involved in *p*-aminosalicylic acid resistance in clinical isolates from tuberculosis patients in northern China from 2006 to 2012. Antimicrob Agents Chemother **2015**; 59:1320–4.
10. Schön T, Miotto P, Köser CU, Viveiros M, Böttger E, Cambau E. *Mycobacterium tuberculosis* drug-resistance testing: challenges, recent developments and perspectives. Clin Microbiol Infect **2017**; 23:154–60.

Correspondence: C. U. Köser, Department of Genetics, University of Cambridge, Downing Street, Cambridge CB2 3EH, United Kingdom (cuk21@cam.ac.uk).

Clinical Infectious Diseases® 2018;66(9):1481–2

DOI: 10.1093/cid/cix1042

Invasive Fungal Sinusitis due to Mucor Species in a Patient on Ibrutinib

To the Editor—We read with interest the recent article by Chamilos et al regarding the risk of invasive fungal infection (IFI) associated with small molecule kinase inhibitors (SMKIs) [1]. In heeding the authors' call for publication of such cases, we briefly present the case of a patient recently evaluated by our transplant infectious diseases service with invasive fungal sinusitis due to Mucorales.

Our patient was a 79-year-old man with chronic lymphocytic leukemia (CLL), well-controlled diabetes mellitus (hemoglobin A1c 6.9%), and coronary artery disease who presented with 3 weeks of progressive right maxillary sinus pain and fever. He was diagnosed with CLL 5 years prior and had intermittently required transfusions of red blood cells and platelets until initiating ibrutinib 17 months prior to presentation. He was hospitalized for community-acquired pneumonia once within the last 5 years but had no other history of severe or unusual infections. Computed tomography of his sinuses showed near-complete opacification of the right maxillary, ethmoid, and sphenoid sinuses. There was a small subperiosteal abscess extending through the inferior orbital wall adjoining an inferior orbital abscess. He was taken emergently to the operating room by otolaryngology and ophthalmology. He underwent right maxillary antrostomy, maxillectomy, and infratemporal fossa resection. All frozen sections showed angioinvasive fungal disease. A small length of tubing from an external ventricular drain device was tunneled inferolaterally into the orbit to instill intraorbital antifungal therapy. He was started on intravenous liposomal amphotericin B and isavuconazole along with amphotericin-soaked packing and twice-daily intraorbital infusion of amphotericin. Cultures from the sinus tissue yielded growth of a fluffy white mold within 72

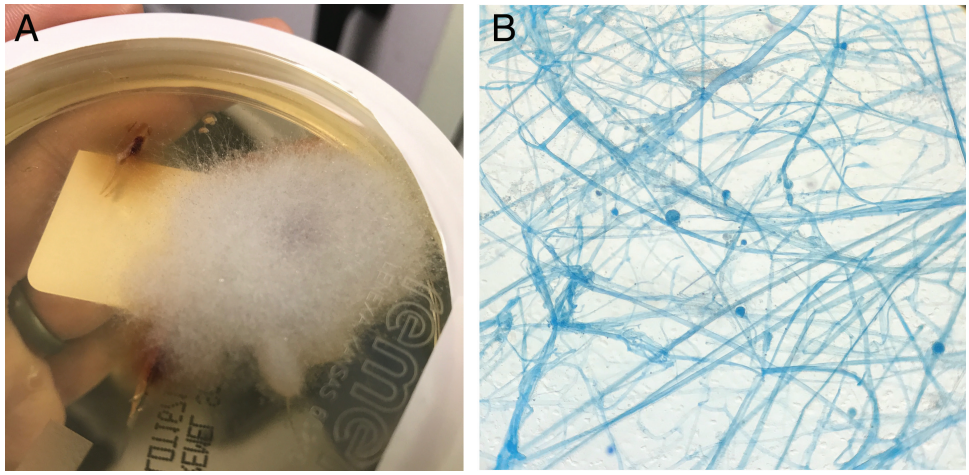

Figure 1. *A*, Fungal culture at 30°C after approximately 72 hours. *B*, Tease preparation of the mold using lactophenol cotton blue stain.

hours (Figure 1A). Microscopic evaluation of a tease preparation of the mold revealed aseptate nonpigmented hyphae, eventually identified as mucor species (Figure 1B). Intravenous amphotericin was discontinued after 7 days of dual systemic antifungal therapy.

His ibrutinib was discontinued at the time of admission out of concern for its contribution to his infection. His complete blood count was notable for pancytopenia along with absolute neutropenia and lymphocytopenia with nadirs of 520 cells/μL and 320 cells/μL, respectively, for which he was given granulocyte colony-stimulating factor. His total immunoglobulin G level was 207 mg/dL (normal range, 694–1618 mg/dL) for which he received intravenous immunoglobulin. He was discharged in stable condition after 17 days. At 2-month follow-up in clinic, he continues to improve with mild residual sinus pain and persistent cytopenias. We plan for an extended course of isavuconazole followed by indefinite mold prophylaxis if he restarts an SMKI.

After review of case reports of IFI related to ibrutinib, we believe this represents the first reported case of invasive fungal sinusitis with biopsy-proven Mucorales related to an SMKI. As noted in the viewpoint, IFI related to SMKIs will likely become more widespread as their use and indications expand. As infectious disease physicians, we must expand our differential diagnoses in patients on SMKIs to include opportunistic infections classically associated with more significant levels of immunosuppression.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Financial support. D.P.S. is supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) under Award Number UL1TR002378 and TL1TR002382.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

David Phillip Serota, Aneesh K. Mehta, and Varun K. Phadke

Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia

Reference

1. Chamilos G, Lionakis MS, Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. Clin Infect Dis **2018**; 66:140–8.

Correspondence: D. P. Serota, Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, 49 Jesse Hill Jr Drive Southeast, Atlanta, GA 30303 (dserota@emory.edu).

Clinical Infectious Diseases® 2018;66(9):1482–3

DOI: 10.1093/cid/cix1058

Economic Impact of a Preferred Anti-Methicillin Susceptible *Staphylococcus aureus* Protocol

To the Editor—Recently the work of McDanel et al. [1] was published in *Clinical Infectious Diseases*, which studied over 3000 Veterans Affairs (VA) patients in 119 VA facilities, finding cefazolin therapy may offer a mortality benefit over nafcillin or oxacillin for treatment of methicillin-susceptible *Staphylocccus aureus* (MSSA) infections complicated by bacteremia. This important study contributes to a growing body of literature supporting the use of cefazolin over an anti-staphylococcal penicillin, even for complicated infections [1–6]. Although we applaud the authors for their work, we feel they have left an important piece of information out of their discussion. The economic impact of using cefazolin over oxacillin can be substantial in this time when most workhorse antibiotics are low-cost. To highlight this topic, we provide data from the Miami VA Medical Center.

Data provided here were extracted from a quality assurance report presented to our local antimicrobial stewardship program subcommittee. The appropriate approvals were obtained prior to submission of this work. Days of therapy are not included, and rounded numbers are utilized to prevent disclosure of confidential contractual data.