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COMMENTARY

Fungemia Surveillance in Denmark Demonstrates Emergence of Non-*albicans Candida* Species and Higher Antifungal Usage and Resistance Rates than in Other Nations

Mariana Castanheira[a]

[a]JMI Laboratories, North Liberty, Iowa, USA

ABSTRACT Recent changes in the occurrence of fungal species and the difficulties in performing reference antifungal susceptibility testing highlight the importance of surveillance of fungal organisms and antifungal resistance rates. K. M. T. Astvad et al. report results from recent (2012 to 2015) fungemia surveillance in Denmark and compare the results to previous data (2004 to 2011), showing a decrease in *Candida albicans* infections accompanied by an increase in *C. glabrata* and *C. dubliniensis* infections (J Clin Microbiol 56:e01564-17, 2018, https://doi.org/10.1128/JCM.01564-17). Azole resistance among *C. tropicalis* and *C. parapsilosis* isolates and echinocandin resistance in *C. krusei* isolates were higher in Denmark than in other regions. Interestingly, the usage of antifungals is higher in Denmark than in other Nordic countries.

Invasive antifungal infections (IFI) afflict patients that are vulnerable, including those who are immunocompromised, those with severe underlying illnesses, and those in the extreme age groups (1, 2). These infections have a high associated mortality rate that can be close to 50% (3), and the correct diagnosis and prompt administration of appropriate antifungal therapy are crucial to diminish these rates (2).

Knowing the epidemiology of fungal species and the activity of antifungal agents tested against these pathogens on a local level is critical for the clinical management of IFIs, since diagnosing IFIs can be challenging due to multiple factors that include the nonspecific clinical manifestations (4). Culture-based methods might require 48 h or longer to provide results, and these methodologies have low sensitivity for detecting various rare yeast and all filamentous fungus species and are often reported as unreliable (4–6). Furthermore, even when the organism is cultured, the antifungal susceptibility testing is delayed since it is usually performed by referral laboratories and requires highly trained personnel. Developing laboratory testing that targets fungal biomarkers to indicate the presence of fungal infection and DNA-based methodologies to detect organisms causing IFI is an important advancement, providing timely and reliable results; however, these methods are expensive and not available in most clinical laboratories (7).

This landscape highlights the need for surveillance initiatives on the local and global levels to monitor the occurrence of IFI and changes in the prevalence of fungal species and in antifungal susceptibility patterns for organisms causing IFI. Surveillance programs are scarce due to their complexity, costs, and limitations that can involve collecting adequate clinical data, availability of support information such as antifungal consumption, and application of reference and state-of-the-art laboratory methods for organism identification and emergence of resistance.

In this issue of the *Journal of Clinical Microbiology*, Astvad et al. report data from a Danish fungemia surveillance from 2012 to 2015 and compare these results to 12 years of published fungemia data (8). The authors analyzed the prevalence in the overall

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Address correspondence to mariana-castanheira@jmilabs.com.

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population of 1,883 fungemia episodes observed in 13 Danish hospitals during the study period.

The incidence of fungemia did not increase in the study period compared to prior years; however, episodes increased in male patients and in those who were 80 to 89 years of age. The authors also observed a decrease in the occurrence of *C. albicans*, although this organism still comprised close to 50% of the isolates recovered. This finding was accompanied by increases in the number of *C. glabrata* infections, which were more common among females and as patient age increased. Changes in the prevalence of *Candida* species causing IFI have been recently observed by other authors (9), and, in the case of *C. glabrata*, this change might impact the selection of antifungal chemotherapy since this organism exhibits rates of resistance to azoles and echinocandins as high as 8.0% and 0.5% (10), respectively, whereas resistance to these antifungal classes in *C. albicans* is uncommon. Other interesting findings were the increase in the incidence of *C. dubliniensis* infections and the association of *C. tropicalis* and male patients.

The authors report organism identification and susceptibility testing results performed in a central laboratory for almost 2,000 fungal isolates collected during the study period. Testing surveillance isolates in a central reference laboratory has been considered optimal and has been recommended by an expert panel assembled as part of the American Society for Microbiology (ASM) Task Force on Antimicrobial Resistance (11). This practice ensures the use of the reference methodologies with quality assurance that is monitored at the same level for the duration of the study. Furthermore, the practice warrants that isolates will be available for follow-up testing when needed or when those methods become available.

Susceptibility testing results demonstrated a statistically significant decrease of rates of susceptibility to azoles among *Candida* species from 65.2% in 2008 to 2011 to 60.6% in 2012 to 2015. Among the most common *Candida* species, resistance rates ranged from 0.4% for *C. albicans* to 9.1% for *C. glabrata*. Azole resistance in *C. tropicalis* and *C. parapsilosis* was approximately 6.0%. These rates are considerably higher than those seen in results from a global surveillance collection from 2014 to 2015, which displayed overall fluconazole resistance rates of 2.7% and 3.8% in *C. tropicalis* and *C. parapsilosis*, respectively, and were 4.4% and 1.6% in analyzing the European subset of this global collection (10). Echinocandin resistance also increased among Danish isolates from 0.0% in 2004 to 2007 to 0.6% in 2008 to 2011 and 1.7% in 2012 to 2015. Echinocandin resistance was higher in *C. kefyr* (23%; 3/13 isolates), followed by *C. krusei* (6.8%), while 2.7% of the *C. glabrata* isolates were resistant to this antifungal class. Echinocandin resistance among *C. krusei* was higher in this study than in worldwide data that did not detect resistance among 142 *C. krusei* isolates collected during 2013 (12) and 2014 to 2015 (10).

The results for Danish isolates were generated using the EUCAST reference method (13) and have minor differences from those generated by the Clinical Laboratory and Standards Institute (CLSI) method (14, 15). These 2 reference methods are similar in many aspects, but they differ in inoculum concentration, in the glucose content of the medium, and in the use of round-bottom versus flat-bottom microdilution plates and of visual versus spectrophotometric endpoint reading for yeasts. More importantly, the methods have separate breakpoint criteria; however, results for the methodologies and for most combinations of antifungal agents and fungal species were shown to be comparable within a ± 2 dilution essential agreement (16–20).

Lastly, the authors captured in the correlation that antifungal usage in Denmark has been stable in the last few years for all antifungals, with the exception of posaconazole. Interestingly, antifungal consumption in Denmark is much higher than in other Nordic countries, and one can only speculate on the reasons for these differences and on whether the elevated usage of antifungals could have affected the elevated resistance rates observed for certain *Candida* species that differ from global and European data (10).

Many tools available to help manage bacterial infections are not available for fungal diseases, including information to assist the judicious use of antifungal agents. This gap in information and/or resource availability is often filled by data from surveillance. The surveillance data reported by Astvad et al. will raise awareness of the changes of species distribution and of the specific azole and echinocandin resistance issues noticed in this population. This Danish study and other surveillance programs are extremely valuable to assist the empirical treatment of serious infections, including IFIs, that impact quality of life, generate long-term disability, and have elevated costs for the patients and health care systems (5).

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