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COMMENTARY

Insights into the Unique Nature of the East Asian Clade of the Emerging Pathogenic Yeast *Candida auris*

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ABSTRACT The emerging yeast *Candida auris* can be highly drug resistant, causing invasive infections, and large outbreaks. *C. auris* went from an unknown pathogen a decade ago to being reported in over thirty countries on six continents. *C. auris* consists of four discrete clades, based on where the first isolates of the clade were reported, South Asian (clade I), East Asian (clade II), African (clade III), and South American (clade IV). These clades have unique genetic and biochemical characteristics that are important to understand and inform the global response to *C. auris*. Clade II has been underrepresented in the literature despite being the first one discovered. In this issue of the *Journal of Clinical Microbiology*, Y. J. Kwon et al. (J Clin Microbiol 57:e01624-18, 2019, https://doi.org/10.1128/JCM.01624-18) describe the largest collection of clinical isolates from Clade II, which is also the longest-running span of clinical cases, 20 years, from any single region to date. Clade II appears to have a propensity for the ear that is uncharacteristic of the other clades, which typically cause invasive infections and large-scale outbreaks. This study provides new information on an understudied lineage of *C. auris* and has important implications for future surveillance.

Candida auris is an emerging and often multidrug-resistant yeast that can cause invasive as well as superficial infections. Unlike most other *Candida* species, *C. auris* can spread among patients in hospitals and nursing homes, causing outbreaks (1). Its ability to colonize the patient's skin and other body sites indefinitely, contaminate the patient's environment, and persist for weeks in the health care environment likely contribute to its transmission (1, 2). Moreover, controlling outbreaks of *C. auris* in the health care setting is challenging because many commonly used environmental disinfectants have suboptimal activity against *C. auris* (3).

C. auris was first described in 2009 after being isolated from the ear discharge (hence the name *auris,* Latin for "ear") of a patient in Japan (4). This report was quickly followed by a study from South Korea describing 15 *C. auris* ear isolates collected during 2004 to 2006, which were originally misidentified as *Candida haemulonii* (5). The earliest confirmed isolate of *C. auris* was from a blood culture from 1996, retrospectively identified in a Korean isolate collection (6). After the 2009 description of the type specimen, reports of *C. auris* causing numerous invasive bloodstream infections were published from India and South Africa (7, 8). *C. auris* cases and outbreaks have now been reported in over 30 countries on six continents. In some hospitals, *C. auris* has become the leading cause of candidemia (9). A retrospective review of isolate collections, such as the SENTRY culture collection, indicates *C. auris* has likely emerged globally in the last decade (10).

The rapid pace at which *C. auris* has been detected across the world and strong evidence of transmission in health care settings has led to a realization that a global effort is needed to control this novel pathogen (1). A robust response to this pathogen

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requires a more comprehensive understanding of its epidemiology, development of diagnostics, establishment of antifungal susceptibility testing breakpoints or epidemiological cutoff values (ECVs), efficacy data on disinfectants, and identification of the mechanisms of transmission. In order to accomplish these priorities, we must first improve our understanding of the diversity and biology of *C. auris* (4).

Whole-genome sequence (WGS) analysis indicates that the worldwide *C. auris* population consists of four phylogenetically distinct clades. Each clade is strongly associated with distinct geographic regions and differs from other clades by tens of thousands of single-nucleotide polymorphisms (SNPs), while the genetic diversity within a clade is extremely low (10). These clades are most often referenced by the geographic region they were first associated with clade I (South Asia), clade II (East Asia), clade III (Africa), and clade IV (South America) (10–12). In the age of globalization and international travel, it is important to note that without a definitive origin or a comprehensive evolutionary rate analysis, this geographic distribution could be the result of importation and local spread rather than reflecting the origination points of these clades (13).

Every major clade except for clade II has been linked to outbreaks with invasive infections. Extensive WGS analysis has shown that the current epidemic in the United States is dominated by clade I and clade IV, but infections attributed to all four clades have been identified in the United States (14). Eight of these clinical cases have travel-related epidemiological links, indicating that initial travel-related cases seeded the U.S. *C. auris* population. Clades I and III predominate in European outbreaks studied to date (12, 15, 16). Because fewer clinical isolates have been recovered from clade II, there is a substantial gap in in *C. auris* research to date, and it is therefore poorly understood relative to the other clades. The recent article by Kwon and colleagues (J Clin Microbiol 57:e01624-18, https://doi.org/10.1128/JCM.01624-18) helps fill this gap by describing 61 clinical isolates from clade II, constituting the largest collection from this clade to date. This collection includes isolates collected from 13 hospitals over 20 years.

The description of these cases offers valuable insights into the clinical and epidemiological characteristics of clade II. Of the 61 clade II isolates described by Kwon and colleagues, 57 (>93%) were isolated from ear infections. Other clades of *C. auris* primarily cause invasive infections and are rarely reported from ear infections. The reason for this observation may be that clade II has a propensity for ears or may be caused by biases arising from variations in laboratory testing practices. For example, it is common practice in most clinical settings to perform isolation and identification to the species level from sterile sites, while fungi from nonsterile sites such as the ear are rarely identified to the species level. Nevertheless, the dearth of reported invasive infections from clade II and the propensity of this clade to cause ear infections is noteworthy. Kwon et al. report no apparent clusters in time or by hospital over the 20-year time period; however, this was not a comprehensive surveillance effort for *C. auris* in South Korea. In contrast, strong evidence of health care-associated transmission exists for the other *C. auris* clades and for rapid increases in the number of cases. Case in point, the number of cases reported from Gauteng Province, South Africa climbed from 18 during October 2012 to November 2013 to 861 cases during the same time period 3 years later (7). Most cases were caused by clade III strains, and the majority of isolates were from urine, blood, or other invasive sites; there were no reported ear infections (7). Similarly, in Spain, at the La Fe University Hospital, 112 cases were identified from 2016 to 2018, primarily bloodstream infections and without a single reported ear culture. Moreover, of >1,500 cases of *C. auris* infection and colonization in the United States, only three isolates have been from clade II; two were from ears (17) and one was from a superficial wound. Before this study, limited anecdotal reports, including the original description of the type strain, have hinted at an association of clade II with ear infections or colonization. The data provided by Kwon and colleagues corroborate this hypothesis.

The rapid and recent emergence of *C. auris* has created numerous challenges for

public health response efforts, particularly with respect to diagnostics. The inability of some established yeast identification platforms to recognize *C. auris* has led to widespread misidentification and undetected outbreaks across the world (18). Clade-specific differences may diminish the ability to accurately identify this species. To facilitate progress in these areas, the CDC's Antibiotic Resistance (AR) Laboratory Network supports nationwide laboratory capacity to rapidly detect *C. auris* and provides an AR Isolate Bank panel of 10 *C. auris* isolates (19) (https://wwwn.cdc.gov/arisolatebank/). Recently, substantial progress has been made for diagnostics, including improved isolation techniques (2), multiple PCR, and culture-independent methods (20–22). Updated libraries or databases for established automated identification systems and MALDI-TOF platforms have also improved identification. However, in all this work, isolates from clade II are minimally represented. The article by Kwon and colleagues helps fill this gap by evaluating MALDI-TOF identification and providing antifungal susceptibility testing (AFST) data on 61 isolates from clade II.

In evaluating MALDI-TOF performance, Kwon and colleagues observed that the Biotyper and Vitek MS systems correctly identified 83.6% and 93.4% of their isolates, respectively, with no misidentifications. For the Vitek MS, they also evaluated an *in vitro* diagnostic library (Vitek *in vitro* diagnostics [IVD] 3.2), which included additional *C. auris* references that improved accurate identification up to 96.7%, thus demonstrating that MALDI-TOF performance is dependent on the reference database used. Although not FDA cleared for patient use, multiple MALDI-TOF libraries, such as the CMdb database (23), MicrobeNet, or in-house databases like the Wadsworth MALDI-TOF library (17), that consist of reference spectra consisting of strains from all four clades can provide improved identification. The freely available MicrobeNet database is validated by CDC experts (https://www.cdc.gov/microbenet/index.html) and is a valuable resource especially given access to MALDI-TOF libraries can be limited. This database currently has eight *C. auris* reference spectra and can be used to retrospectively analyze MALDI-TOF spectra results.

Based on the antifungal susceptibility testing (AFST) results for the 61 isolates presented by Kwon et al. and by previous reports, clade II appears to be less resistant to antifungals than other clades. Clades I, III, and IV have been observed to be resistant to multiple antifungal drugs, with some isolates resistant to all three major antifungal classes (azoles, polyenes, and echinocandins) (24), and levels of antifungal resistance vary widely across the three clades. Interestingly, only 7% of the fluconazole-resistant isolates in this study harbored amino acid substitutions in the *ERG11* gene that are typically associated with azole resistance (25). The authors contrast this with the CDC's *C. auris* AR Isolate Bank panel, in which all fluconazole-resistant isolates have *ERG11* point mutations. This observation is highly relevant to surveillance efforts aimed at detecting azole resistance through *ERG11* mutations because there are multiple mechanisms for resistance in *C. auris*.

There are no established *C. auris*-specific breakpoints for AFST, and therefore data based on closely related species have been used to implement temporary AFST guidelines to compensate for the absence of ECVs or clinical breakpoints (https://www.cdc.gov/fungal/candida-auris/c-auris-antifungal.html). Nearly all laboratories rely on automated systems for routine AFST. These systems are attractive because they can reduce the laboratory workload relative to that for CLSI manual broth microdilution methods, but they often underperform. Although Kwon and colleagues' evaluation of the Vitek 2 for AFST observed essential (96.7%) agreement with CLSI methods for fluconazole, others have reported suboptimal performance for amphotericin B (26), and a cautionary approach is warranted for automated AFST systems.

Efforts to control *C. auris* have posed multiple challenges, which include developing and evaluating of new diagnostics, understanding its epidemiology, and identifying means to minimize transmission among patients. Knowledge about clade-specific information is crucial to support the global effort to control this pathogen. The recent article by Kwon and colleagues contributes to this goal by providing referable data on 61 *C. auris* isolates from a less well-studied phylogenetic clade. Ongoing research is

needed to improve our understanding of *C. auris* and inform prevention efforts, and this work should continue to include isolates from all clades. CDC's *C. auris* AR Isolate Bank, which includes isolates from all four clades of *C. auris*, can help facilitate research by providing a diverse set of commonly studied strains for comparing results. Together with the MicrobeNet database, these are valuable tools for developing new identification methods, therapies, and disinfectants, and for conducting basic research on *C. auris*.

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