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EDITORIAL COMMENTARY

Emergence of *Candida auris*: An International Call to Arms

Cornelius J. Clancy[1,2] and M. Hong Nguyen[1,3]

[1]Department of Medicine, University of Pittsburgh, [2]VA Pittsburgh Healthcare System, and [3]University of Pittsburgh Medical Center, Pennsylvania

(See the Major Article by Lockhart et al on pages 134–40.)

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On June 24, 2016, the Centers for Disease Control and Prevention (CDC) issued an extraordinary alert, advising US healthcare facilities "to be on the lookout for *Candida auris* in patients" [1]. The alert noted that *C. auris* infections had been identified in several countries since 2009. Although cases have not been described in the United States, CDC reported that a *C. auris* isolate from 2013 was detected during ongoing surveillance. Within a week, Public Health England (PHE) announced that *C. auris* was recovered from healthcare facilities in that country, and 1 hospital has been managing an outbreak involving more than 40 patients in an intensive care unit (ICU) since April 2015 [2]. The outbreak persisted despite regular patient screening, environmental decontamination, ward closure, and other enhanced infection control interventions [2]. In this issue of *Clinical Infectious Diseases*, Lockhart and colleagues describe the study that prompted the CDC alert [3].

Reports of *C. auris* infections have been published from Japan, South Korea, India, South Africa, Kuwait, and Venezuela, describing 45 patients with candidemia and 26 patients with other invasive diseases or colonization [4–11]. The earliest case to date was identified in retrospect by DNA sequencing of a Korean bloodstream isolate from 1996 [6]. These studies established salient features of *C. auris* invasive infections. *Candida auris* is typically misidentified by commercial API-20C or Vitek-2 systems (Table 1). Infections often occur as part of nosocomial outbreaks. Patients range from neonates to the elderly and have well-recognized risk factors for invasive candidiasis. A large majority of isolates are fluconazole resistant, and amphotericin B and echinocandin resistance rates are approximately 30%–40% and approximately 5%–10%, respectively. Almost half of isolates are multidrug resistant (MDR; resistant to 2 or more antifungal classes), and a small percentage is pandrug resistant. Optimal treatment regimens are unknown. Mortality rates are high, approaching 70% during candidemia.

CDC investigators were aware of these data when they determined that an outbreak of yeast infections at a hospital in Pakistan in 2015 was caused by *C. auris*, rather than *Saccharomyces cerevisiae* as initially believed. As detailed by Lockhart et al, CDC assembled an international consortium to describe the epidemiology of *C. auris* infections and compare whole genome sequences of *C. auris* isolates. The investigative team collected isolates from 54 patients in 18 Pakistani, Indian, South African, and Venezuelan hospitals, and they collected clinical data from 41 patients.

Epidemiologic, microbiologic, and clinical findings from this study corroborate those of previously published reports, as summarized above [4–11]. Three results provide important new insights. First, phylogenetic analysis of whole genome sequences revealed 4 distinct *C. auris* clades, which were comprised exclusively of isolates from Pakistan–India, South Africa, Venezuela, or Japan (the 2009 type specimen). Almost all isolates within a given phylogeographic clade were highly clonal, differing by fewer than 70 genome-wide single nucleotide polymorphisms. Second, specific *ERG11* azole–resistance mutations were shared by isolates within clades. Third, a query of >15 000 Candida isolates deposited in the worldwide SENTRY repository since 2004 uncovered only 4 misidentified *C. auris* from 2009, 2013, 2014, and 2015. The authors reasonably conclude that antifungal-resistant *C. auris* is likely to have emerged recently, independently and almost simultaneously on 3 continents, rather than as a result of worldwide dissemination of a dominant clone. However, the data also indicate that clonal isolates are distributed over large distances within countries and continents. The evidence for hospital outbreaks and clonal spread suggests that *C. auris* infections may differ from invasive candidiasis due to most other Candida species, which is usually sporadic and caused by genetically distinct, endogenous isolates that are colonizing the patient's gastrointestinal tract, mucosal surfaces, or skin [13].

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Correspondence: C. J. Clancy, 3550 Terrace Street, Scaife Hall 867, Pittsburgh, PA 15261 (cjc76@pitt.edu).

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Table 1. Laboratory Testing and Misidentification of *Candida auris*

Diagnostic System	Comments
Antifungal Susceptibility Testing Method	
API-20C	May misidentify *Candida auris* as *Rhodotorula glutinis, Candida sake, Saccharomyces cerevisiae*
Vitek-2	May misidentify *C. auris* as *Candida haemulonii, Candida famata*
Matrix-assisted laser desorption/ionization-time of flight mass spectrometry	Will identify *C. auris* if appropriate sequences are in the database. The Bruker Biotyper library has 3 isolates from Japan and South Korea in its database. If sequences are not in the database (eg, US Food and Drug Administration database), isolates will be identified as yeast that gives no score.
DNA sequencing	Sequencing of the internal transcribed spacer and D1-D2 domain of the large subunit rRNA gene has been performed most commonly.
Clinical and Laboratories Standards Institute broth microdilution method	May give falsely elevated caspofungin MICs
Vitek-2	May give falsely elevated amphotericin B MICs
Etest	May give most consistent results

The table is based on data from [12].

Abbreviation: MIC, minimum inhibitory concentration.

Why has *C. auris* generated such concern among public health agencies? The fear is that biologic and epidemiologic factors are aligned for more extensive, worldwide emergence and/or dissemination of *C. auris* infections. The following 2, nonmutually exclusive scenarios could result in a major global public health problem: various *C. auris* lineages, in particular MDR lineages, may continue to emerge independently and spread clonally in countries that are currently affected and as-yet unaffected and 1 or more dominant MDR clones may disseminate intercontinentally. Although Lockhart et al did not describe the latter phenomenon, growing cohorts of colonized and infected patients in countries with large populations and far-reaching international diasporas attest to its feasibility. In troubling publications from India, *C. auris* already accounted for >5% of candidemia in a national survey of ICUs and as much as 30% of candidemia at individual hospitals [8, 14]. Other properties of *C. auris* may contribute to this perfect storm, including difficulties in timely and definitive identification by commonly used commercial methods, intrinsic virulence that may be similar to *C. albicans* rather than attenuated like most non-*C. albicans* species [15], the ability to cause lengthy outbreaks and possibly persist within hospital environments, and occupancy of as-yet unidentified ecological niches. If events come together, we could witness the fungal counterpart to the worldwide expansion of carbapenem-resistant Enterobacteriaceae.

Why is *C. auris* emerging now? The SENTRY data argue against the presence of widespread, previously unrecognized cases prior to 2009. Lockhart et al. speculate that increased availability of antifungal agents may have played a role. However, antifungal selection is unlikely to be the sole determinant, as non-*C. albicans* species have increased in prevalence since fluconazole was introduced in 1990, without prior emergence of *C. auris* [16]. It is conceivable that changes to *C. auris*' ecological niches have brought the fungus into greater contact with susceptible humans. At the same time, the species has intrinsic features that are well suited to pathogenesis. A draft genome revealed large percentages of genes devoted to central metabolism [17], a property that is common to pathogenic *Candida* and crucial for adaptation to highly divergent environments. *Candida auris* shares numerous virulence attributes with *C. albicans*, including genes and pathways involved in cell wall modeling and nutrient acquisition, histidine kinase-2 component systems, iron acquisition, tissue invasion, enzyme secretion, and multidrug efflux [17]. Interestingly, *C. auris* is a particularly close phylogenetic relative of *Candida krusei* and *Candida lusitaniae*, species notable for intrinsic or inducible antifungal resistance [17–19]. *Candida auris* also demonstrates hardy phenotypes such as salt tolerance and cell aggregation into large, difficult-to-disperse clusters, which may promote survival in hospital environments [4, 15]. Moreover, isolates exhibit the thermotolerance necessary to infect humans, growing optimally at 37°C and maintaining viability at up to 42°C [4]. It is possible that 1 or more of these attributes adapted recently and combined with preexisting properties and/or environmental changes to allow expansion into new niches. A central question is whether conditions that support *C. auris*' emergence are specific to geographic locations in which it has been described.

Lockhart et al.'s article is a call to arms for the international medical community to attack the *C. auris* challenge before it escalates further. Guidance for *C. auris* reporting, detection, infection control, and environmental cleaning is available through the CDC, PHE, and the Public Health Agency of Canada [1, 2, 20]. A summary of laboratory testing methods and potential misidentification of *C. auris* is presented in Table 1. Multidisciplinary research into *C. auris* should be modeled after remarkable successes in investigating the emergence of *Cryptococcus gattii* in previously nonendemic areas [21]. Immediate priorities are to better understand traditional and genomic epidemiology, ecology, evolution, resistance mechanisms, and treatment and prevention. We are living in an era in which

fungal diseases are causing unprecedented damage to animals, plants, and ecosystems [22]. The *C. auris* story is another reminder that humans will not be spared from emerging mycoses.

Addendum prior to publication. Two papers have been published since the acceptance of this editorial commentary, which provide details on the English *C. auris* outbreak and the first cases of *C. auris* infection in the US [23, 24] Both papers report on transmission of *C. auris* within healthcare settings, and they highlight the importance of persistent colonization of hospital environments and multiple body sites of patients by *C. auris*. The latter paper, which describes 7 patients from 4 states, also presents the first evidence for inter-continental spread of *C. auris*, as several US isolates were very closely related to South Asian or South American clones by whole genome sequence analysis [24].

Note

Potential conflicts of interest. Both authors: no reported conflicts. Both 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

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