Simultaneous Emergence of Multidrug-Resistant *Candida auris* on 3 Continents Confirmed by Whole-Genome Sequencing and Epidemiological Analyses

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(See the Editorial Commentary by Clancy and Nguyen on pages 141–3.)

Background. *Candida auris*, a multidrug-resistant yeast that causes invasive infections, was first described in 2009 in Japan and has since been reported from several countries.

Methods. To understand the global emergence and epidemiology of *C. auris*, we obtained isolates from 54 patients with *C. auris* infection from Pakistan, India, South Africa, and Venezuela during 2012–2015 and the type specimen from Japan. Patient information was available for 41 of the isolates. We conducted antifungal susceptibility testing and whole-genome sequencing (WGS).

Results. Available clinical information revealed that 41% of patients had diabetes mellitus, 51% had undergone recent surgery, 73% had a central venous catheter, and 41% were receiving systemic antifungal therapy when *C. auris* was isolated. The median time from admission to infection was 19 days (interquartile range, 9–36 days), 61% of patients had bloodstream infection, and 59% died. Using stringent break points, 93% of isolates were resistant to fluconazole, 35% to amphotericin B, and 7% to echinocandins; 41% were resistant to 2 antifungal classes and 4% were resistant to 3 classes. WGS demonstrated that isolates were grouped into unique clades by geographic region. Clades were separated by thousands of single-nucleotide polymorphisms, but within each clade isolates were clonal. Different mutations in *ERG11* were associated with azole resistance in each geographic clade.

Conclusions. *C. auris* is an emerging healthcare-associated pathogen associated with high mortality. Treatment options are limited, due to antifungal resistance. WGS analysis suggests nearly simultaneous, and recent, independent emergence of different clonal populations on 3 continents. Risk factors and transmission mechanisms need to be elucidated to guide control measures.

Keywords. *Candida auris*; candidemia; fluconazole resistance; amphotericin B resistance; whole genome sequence typing.

The yeast *Candida auris* was described in 2009 after being recovered from the external ear canal of a patient in Japan [1] and was subsequently recognized as causing otitis media in 15 patients from 5 hospitals in Korea [2]. Two years later, a report from South Korea described 3 bloodstream infections (BSIs) caused by *C. auris* [3], establishing that this new species was capable of causing invasive infections. Shortly thereafter, *C. auris* fungemia from several hospitals in India [4–6], South Africa [7], and Kuwait [8] was described.

C. auris exhibits resistance to fluconazole and variable susceptibility to other azoles, amphotericin B, and echinocandins. It phenotypically resembles *Candida haemulonii* and requires use of molecular methods for identification [9, 10]. *C. auris* can be a challenge to identify and treat, especially in resource-limited settings, where molecular identification may not be immediately available and access to antifungals other than fluconazole may be limited.

In 2015, the US Centers for Disease Control and Prevention (CDC) was asked to assist with an outbreak of BSIs and positive urine cultures caused by presumed *Saccharomyces* at a hospital in Pakistan. The isolates were shipped to the CDC, where they were identified as *C. auris*, which had not previously been reported from Pakistan. At the same time, the CDC was aware of increasing numbers of cases of *C. auris* infections in both India and South Africa [4, 6, 7] and was subsequently notified

of cases from Venezuela [11]. An international collaboration was established to better understand the epidemiology of *C. auris*, determine the extent of resistance and whether the emergence of this organism was occurring independently in multiple countries or was caused by the spread of a single outbreak strain. Here we report clinical characteristics of patients with *C. auris* infection, antifungal susceptibility patterns, and results of whole-genome sequence (WGS) analysis of *C. auris* isolates.

METHODS

Case Patient Information
Case patient information was obtained using a standardized surveillance case report form and was available for 41 (76%) of the 54 patients with isolates. The CDC's National Center for Emerging and Zoonotic Infectious Diseases determined that this project constituted a nonresearch public health surveillance activity.

Isolates
Fifty-four isolates from 54 patients during 2012–2015 were collected from Pakistan (n = 18; 2 hospitals), India (n = 19; 3 hospitals), South Africa, (n = 10; 8 hospitals), and Venezuela (n = 5; 1 hospital) (Supplemental Table 1). In addition, the type specimen from Japan was included as was a retrospectively identified Pakistan isolate from 2008. Isolates were from blood (n = 27), urine (n = 10), soft tissue (n = 5), or other sites (n = 12).

DNA Purification and Isolate Identification
DNA was extracted using the ZYMO Research ZR Fungal/Bacterial DNA MiniPrep kit [12]. Species identities were confirmed by sequencing the D1–D2 region of the 28S subunit of ribosomal DNA [13].

Antifungal Susceptibility Testing
Antifungal susceptibility testing was performed as described elsewhere [14]. *C. auris*–specific break points were defined conservatively based on those established for closely related *Candida* species. Because the modal minimum inhibitory concentration (MIC) to fluconazole was at the upper limit of the measured distribution, resistance to fluconazole was arbitrarily set at ≥32 μg/mL. Other break points were ≥2 μg/mL for voriconazole (as for *Candida krusei* [14]), ≥8 μg/mL for the echinocandins (as for *Candida parapsilosis* and *Candida guilliermondii* [14]), ≥128 μg/mL for flucytosine (above the achievable dose), and ≥2 μg/mL for amphotericin B.

WGS, Genomic Assembly, and Single-Nucleotide Polymorphism Identification
Of 54 available isolates, 47 were selected for WGS. To improve assembly, 2 isolates were sequenced using the PacBio platform, and all 47 isolates were sequenced using Illumina HiSeq. Sequencing libraries were prepared as described elsewhere [15]. Two previously published genomes of *C. auris* (ERR899743 and SRR1664627) from India were included [16, 17]. The reference genome was generated by de novo assembly of PacBio reads from isolate B8441, as described elsewhere [18], and used as a reference for single-nucleotide polymorphism (SNP) calling. SNPs were identified using 2 independent pipelines, as described elsewhere (see also the legend to Supplemental Figure 1) [15, 19]. The SNP calls were filtered and included in the final matrix if they were not identified in repetitive regions, were found in <90% of the base calls at that position, and had a minimum read depth coverage of 10. Reads that mapped to multiple locations and indels were excluded. Genome-wide SNP-based phylogenetic analyses was conducted using the maximum parsimony algorithm in MEGA V6.06 software, [20]. Statistical significance of the phylogenetic tree was tested using bootstrap analysis with 1000 reiterations. Read data were deposited into the National Center for Biotechnology Information's Sequence Read Archive under BioProject PRJNA328792.

Azole Resistance Mutation Identification
For resistance gene analysis, orthologous sequences to *Candida albicans ERG11* from SC5314 Assembly 22 (Candida Genome Database; http://www.candidagenome.org/) were extracted from each *C. auris* genome and aligned using a ClustalW alignment in MEGA V6.06 software [20]. Sequences were evaluated for amino acid substitutions that corresponded to those described elsewhere within hot-spot regions in azole-resistant *C. albicans* [21].

Query of a Global Candidemia Surveillance Program for *C. auris*
To understand whether *C. auris* emerged after 2009 or had been overlooked or misidentified in the past, we queried an ongoing international antifungal surveillance program, SENTRY (JMI Laboratories) [22] containing 15 271 candidemia isolates collected from 152 international medical centers during 2004–2015, including from Asia (n = 41), Europe (n = 50), Latin America (n = 15), and North America (n = 46). Isolate identification from 2004 to 2009 was confirmed using a combination of morphological and biochemical tests. After 2009, all uncommon *Candida* species were subject to DNA sequencing and/or matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry [22]. Four presumed *C. haemulonii* (the most common misidentification of *C. auris*) isolates collected before 2009 were retrospectively reidentified as *C. auris* by using MALDI-TOF mass spectrometry.

RESULTS

Case Patient Description
Demographic and clinical information was available for 41 (76%) of 54 patients (Table 1). Nearly half (44%) of the patients with clinical information were from Pakistan (n = 18), 15 (37%) were from India, 5 (12%) were from Venezuela, and 3 (7%) were from South Africa. The median age was 54 years (interquartile range [IQR], 24–69); 3 patients, all from Venezuela, were

Table 1. Demographic and Clinical Characteristics of Patients With _Candida auris_ Infections in Pakistan, India, Venezuela, and South Africa, 2012–2015

Characteristic	Total (n = 41)	India (n = 15)	Pakistan (n = 18)	Venezuela (n = 5)	South Africa (n = 3)
	Patients, No. (%)[a]				
Age, median (IQR), y	54(24–69)	60 (45–79)	48.5 (40–65)	<1 (<1–11)	63 (57–73)
Age category					
Neonates (<28 d)	3 (7)	0	0	3 (60)	0
>28 d to 18 y	3 (7)	0	2 (11)	1 (20)	0
19–64 y	21 (51)	8 (53)	11 (61)	0	2 (67)
≥65 y	14 (34)	7 (47)	5 (28)	1 (20)	1 (33)
Male sex	26 (63)	10 (71)	11 (61)	2 (40)	3 (100)
Underlying conditions					
Diabetes mellitus	17 (41)	9 (60)	7 (39)	0 (0)	1 (33)
Solid tumor	6 (15)	3 (20)	3 (17)	0 (0)	0
Hematological malignancy	0 (0)	0	0	0	0
Liver disease	4 (10)	2 (13)	2 (11)	0	0
Corticosteroid therapy during hospitalization	10 (24)	Unknown	10 (56)	0	0
Other exposures					
Surgery in 90 d before diagnosis of _C. auris_ infection	21 (51)	10 (67)	5 (28)	4 (80)	2 (67)
Central venous catheter	30 (73)	7 (54)	16 (89)	5 (100)	2 (67)
Urinary catheter	25 (61)	8 (62)	16 (89)	Unknown	1 (33)
Antifungal treatment in 90 d before diagnosis of _C. auris_ infection	17 (41)	4 (11)	9 (50)	4 (80)	0
Time from admission to culture, median, (IQR), d	19 (9–36)	19 (9–25)	27 (8–43)	18 (17–24)	19 (13–24)
Site of _C. auris_ infection					
Blood	25 (61)	8 (53)	11 (61)	5 (100)	1 (33)
Urine	7 (17)	0 (0)	6 (33)	0	1 (33)
Respiratory tract	2 (5)	2 (13)	0 (0)	0	
Other	7 (17)	5 (33)	1 (6)	0	1 (33)
Antifungal treatment after _C. auris_ diagnosis					
None	15 (37)	5 (33)	7 (39)	1 (20)	2 (67)
Amphotericin B	15 (37)	2 (13)	10 (56)	2 (40)	1 (33)
Fluconazole	9 (22)	5 (33)	2 (11)	2 (40)	0
Voriconazole	2 (5)	1 (7)	0	1 (20)	0
Caspofungin	8 (20)	6 (43)	0	2 (40)	0
In-hospital deaths	24 (59)	7 (47)	13 (72)	3 (60)	1 (33)

Abbreviation: IQR, interquartile range.

[a]Data represent No. (%) of patients unless otherwise specified.

neonates (≤28 days old); 26 (63%) were male. Diabetes mellitus was the most common underlying condition identified. Half of all patients (n = 21; 51%) had undergone surgery in the 90 days before having a culture yielding _C. auris_; the most common operations included abdominal surgery (n = 6) diabetic limb amputations (n = 5), and cardiac surgery (n = 3). Seventy-three percent (n = 30) had a central venous catheter, and 61% (n = 25) had a urinary catheter. Forty-one percent of patients had received systemic antifungal therapy (primarily fluconazole) in the 90 days before _C. auris_ infection. The median time from admission to diagnosis was 19 days (IQR, 9–36 days).

Fifteen patients did not receive any antifungal treatment and 7 (47%) of those died including 4 of the 5 patients with BSIs who received no treatment. Twenty-six patients received antifungal treatment, and 6 received ≥2 antifungals. Three patients received fluconazole alone, 1 of whom had a BSI and died. Fifteen patients received amphotericin B, 4 of whom had isolates resistant to amphotericin B; 2 patients with amphotericin B–resistant isolates survived while the remaining 2 died. Eight patients were treated with caspofungin, including 1 whose isolate was resistant to caspofungin; 4 of these patients died, including the patient with the echinocandin-resistant isolate.

Overall, 59% (n = 24) of the patients died. Of the 25 patients with BSIs, 17 (68%) died. Of the 7 patients with urinary tract infections, 5 (71%) died, most likely of associated sepsis. Because of the seriousness of the underlying disease of many of the patients, whether and how much C. auris attributed to death could not be determined.

Table 2. Antifungal Susceptibility Data for 54 *Candida auris* Isolates

Antifungal	MIC Range, μg/mL	MIC$_{50}$, μg/mL	MIC$_{90}$, μg/mL
Fluconazole	4–256	128	256
Voriconazole	0.03–16	2	8
Itraconazole	0.125–2	0.5	1
Posaconazole	0.06–1	0.5	1
Caspofungin	0.03–16	0.25	1
Anidulafungin	0.125–16	0.5	1
Micafungin	0.06–4	0.25	2
Flucytosine	0.125–128	0.125	0.5
Amphotericin B	0.38–4	1	2

Abbreviations: MIC, minimum inhibitory concentration; MIC$_{50}$, MIC for 50% of isolates; MIC$_{90}$, MIC for 90% of isolates.

Antifungal Susceptibility Testing

Antifungal susceptibility testing was performed on 54 isolates. The MIC range and the MICs for 50% and 90% of isolates are shown in Table 2, and the MIC distribution is shown in Supplemental Table 2. Using stringent break points, 50 isolates (93%) were resistant to fluconazole, 29 (54%) to voriconazole (≥2 μg/mL), 19 (35%) to amphotericin B (7 from Pakistan and 12 from India), 4 (7%) to echinocandins (2 from India and 2 from South Africa), and 3 (6%) (from India) were resistant to flucytosine. Two isolates, both from India, were resistant to fluconazole, voriconazole, echinocandins, and amphotericin B. In all, 22 (41%) isolates were resistant to ≥2 classes of antifungals.

ERG11 Mutation Analysis

By comparing Erg11 amino acid sequences between *C. albicans* and *C. auris*, 9 amino acid substitutions, which have been identified in resistant but not wild-type *C. albicans* isolates, were identified in all *C. auris* isolates. Three additional hot-spot amino acid substitutions were identified that have been either proposed or proved to significantly increase fluconazole resistance in *C. albicans* [23, 24]. These substitutions were strongly associated with geographic clades: F126T with South Africa, Y132F with Venezuela, and Y132F or K143R with India and Pakistan (Figure 1, Supplemental Table 3).

WGS Analysis

WGS was performed on 47 isolates, including 16 from Pakistan, 15 from India, 10 from South Africa, 5 from Venezuela, and the type specimen from Japan; 2 previously sequenced genomes from National Center for Biotechnology Information's Sequence Read Archive were also included. The assembled genome size was 12.5 Mb, similar to that of other *Candida* species [25].

Reference-based phylogenetic analysis using the NASP pipeline identified approximately 119 000 shared SNPs, of which 86% were parsimoniously informative. Phylogenetic analysis identified a strong phylogeographic structure comprising 4 distinct clades, which were separated by tens of thousands of SNPs and represented distinct geographic regions: South Asia (India/ Pakistan), South Africa, South America (Venezuela), and East Asia (Japan) (Figure 1). Far fewer SNPs were identified within each cluster; for example, <16 SNPs differentiated any 2 isolates from the South American clade, <70 SNPs differentiated any 2 isolates from South Africa, and <60 SNPs differentiated 34 of 36 isolates from South Asia. Two isolates, B8441, the Pakistan isolate from 2008, and B11112, also from Pakistan, differed from the rest of the South Asian strains by >600 SNPs. Furthermore, within the South Asian clade, 2 smaller clusters were identified. These clusters were associated with a single hospital in Pakistan and consisted of nearly identical strains (differences of <2 SNPs). Comparable results were obtained using the GATK pipeline for SNP calling (Supplemental Figure 1).

Candidemia Surveillance

In an effort to test whether *C. auris* had been misidentified or overlooked before the recent emergence, we queried the international surveillance program SENTRY, which contained 15 271 *Candida* isolates collected from 2004 to 2015. Four isolates were identified as *C. auris* (from 2009, 2013, 2014, and 2015), 1 of which had been previously identified as *C. haemulonii*, further supporting the scarcity of *C. auris* before 2009.

DISCUSSION

C. auris is a globally emerging multidrug-resistant yeast that can cause invasive infections. Here we report *C. auris* infections from Pakistan, adding to previous reports from Japan, South Korea, India, South Africa, Venezuela, and Kuwait. Based on the large number of SNPs observed across 47 isolates from 4 regions (South Asia, East Asia, South America, and South Africa) and minimal intraregion genetic diversity, WGS analysis suggests near-simultaneous emergence of *C. auris* in ≥4 locations rather than recent spread from a single source [1, 2, 4, 7, 8]. Although the causes for such emergence are not clear, they may include new or increasing antifungal selection pressures in humans, animals, or the environment.

One possible explanation for the apparent recent emergence of *C. auris* may be that this pathogen has not been previously recognized. To test this hypothesis, we performed a literature review and queried the available global culture collections. Although the first publication of *C. auris* was from 2009, the earliest reported *C. auris* isolate was found in a Korean isolate collection, having come from a 1996 BSI in a pediatric surgery patient [3]. Furthermore, we identified a 2008 *C. auris* isolate from Pakistan, which had not been previously recognized [26]. However, to our knowledge, no other *C. auris* isolates from 1996–2009 have been reported. Our retrospective review of the SENTRY isolate collection, with 15 271 isolates of *Candida* from 4 continents, did not find *C. auris* isolates before 2009 confirming that this pathogen was not simply misidentified previously and was indeed rare. Examination of additional isolate collections from around the world would help to further validate this conclusion.
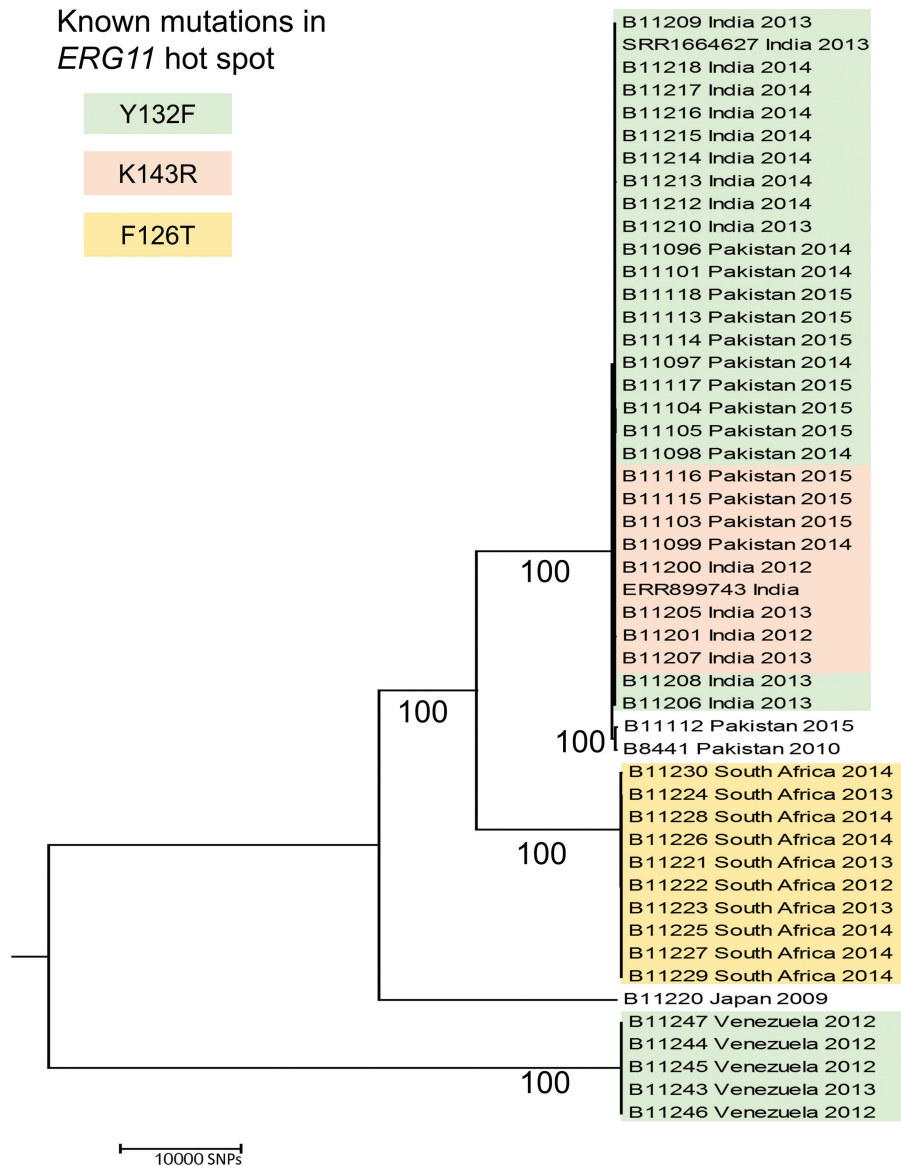
Figure 1. Genetic relationships among isolates inferred using the maximum parsimony method. One of the 2 most parsimonious trees obtained (length, 126 798 base pairs [bp]) is shown. The de novo PacBio assembly, which was used as a reference to identify single-nucleotide polymorphisms (SNPs) in other isolates, contained 20 contigs (11 000–1.4 million bp long; mean length, 623 000 bp; N50 length, 1 million bp). The mean sequencing depth with Illumina was ×235 (range, ×50–×300), which corresponded to 96%–99% coverage of the genome. For all sites, the consistency index is 0.94; the retention index, 0.99; and the composite index, 0.93. Branch lengths were calculated using the mean pathway method and are in the units of the number of changes over the whole sequence. The final data set included a total of 119 188 positions. Numbers below branches show bootstrap values calculated using 500 reiterations. Isolates with known mutations in the hot spot of the ERG11 gene that are associated with azole resistance in Candida albicans are shaded green for Y132F, orange for K143R, and yellow for F126T substitutions. Unshaded isolates have none of these mutations.

Increased clinical availability of antifungal agents may have contributed to the emergence of this organism. Amphotericin B has been available since 1954, fluconazole since 1991, and echinocandins since the early 2000s, but access to these drugs occurred much later in resource-limited settings. Although accurate data on the antifungal prescription practices are difficult to obtain, anecdotal evidence suggests increased use in recent years of triazoles and other antifungals for empiric treatment of surgical and other hospitalized patients. In South Africa, *C. auris* seems to have emerged more rapidly in private-sector hospitals where

echinocandin use is much higher than in public-sector hospitals [27]. Two of the echinocandin-resistant isolate came from South Africa, although neither patient received an echinocandin, suggesting exogenous spread between patients. The fact that a substantial proportion of patients in this investigation were receiving antifungal treatment when *C. auris* infection was diagnosed supports the hypothesis that antifungal selection pressure may, in part, be responsible for the emergence of *C. auris.*

C. auris is phylogenetically related to *Candida* species *krusei, lusitaniae,* and *haemulonii,* which are known to have either

intrinsic or inducible resistance to fluconazole [28], amphotericin B [28], or both [10]. The *C. auris* isolates in the current study exhibit very high MICs for fluconazole, and all but 4 isolates carried amino acid substitutions shown to significantly increase fluconazole resistance [21]. There were no isolates with high MICs (>2 μg/mL) for either itraconazole or posaconazole. Several isolates were shown to have in vitro resistance to the 2 remaining major classes of antifungals, polyenes and echinocandins, suggesting that resistance may be inducible under antifungal pressure. This finding poses an important clinical challenge. A small proportion of isolates demonstrated elevated MICs for all 3 major antifungal classes, severely limiting treatment options.

WGS analysis demonstrated low genetic diversity among isolates within each clade; even across the largest clade of 36 isolates from India and Pakistan, all but 2 isolates differed by <60 SNPs, despite the fact that isolates came from 5 hospitals, thousands of miles apart. A recent WGS study from India with 5 isolates demonstrated similar results [28]. Clonality within *C. auris* has been shown elsewhere using amplified fragment length polymorphism, multilocus sequence typing, and MALDI-TOF mass spectrometry using some of the same Indian isolates from our study [4, 6]; however, the low discriminatory power of those methods did not allow an assessment of genetic relatedness between isolates with identical genotypes [4, 6, 29, 30]. Our WGS analysis shows that the isolates from different regions differed by tens of thousands of SNPs; however, the mean number of SNPs within each geographic cluster was minimal (<70 for isolates within each cluster), again strongly suggesting recent independent emergence.

Our results raise concern that *C. auris* may spread within the hospital setting, evidenced by the presence of nearly identical isolates in 2 hospitals in South Asia. The fact that a majority of patients had a central venous catheter, a urinary catheter, or a recent surgical procedure as possible site of entry, and the timing of infection, a median of 19 days after admission, also support this hypothesis. Like other *Candida* infections, *C. auris* infections seem to be hospital acquired and occur several weeks into a patient's hospital stay, suggesting an exogenous rather than endogenous source and a breach of infection control measures. The overall in-hospital mortality rate of 60% is similar to or higher than those reported from these countries or regions: 52% in Pakistan [26], 44% in India [31], 46% in South Africa [32], and 72% in South America [33]. We were unable to examine time to clearance of infection; however, another study found persistent fungemia up to 3 weeks after initiation of antifungal treatment [4].

The current study has a number of limitations. First, only limited clinical data were available for each patient, and clinical data were not available for all patients whose isolates were included in the study. Second, we were unable to identify risk factors that were specific to *C. auris* because we did not have a comparison group of patients with other *Candida* infections from the same institutions [31]. Third, because there are no universally accepted break points for *C. auris,* antifungal resistance was inferred based on break points for other species. Fourth, extremely low genetic diversity of *C. auris* strains hampered our ability to understand the movement of isolates within each geographic area. Although WGS of isolates from a Pakistani hospital identified 2 subclusters of nearly identical isolates, which was consistent with an ongoing nosocomial outbreak, the exceptionally low diversity among other South Asian isolates made it difficult to establish a relevant cutoff number of SNPs that would differentiate this institutional outbreak from other isolates circulating in the region.

C. auris has been documented in numerous countries on 3 continents in the past 7 years. It is likely that there are other places where this organism is already circulating but has not yet been identified or reported, and it will probably emerge in new locations as well. Multidrug resistance and high associated mortality rates makes *C. auris* an emerging global threat. Of additional concern, *C. auris* may become widely established within certain regions, as evidenced by the fact that it now accounts for nearly 5% of candidemia in Indian intensive care units [5]. There are still many unanswered questions about *C. auris,* including why it has suddenly emerged, whether its clonal expansion and global distribution will level off or continue, how it is transmitted, and what infection prevention and control measures are needed to prevent its spread within hospitals. Further research on risk factors for this infection, how it is acquired and transmitted, and how the fungus develops resistance are needed to control the spread of this pathogen.

Supplementary Data

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

Notes

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