A Candida auris and in an Setting


ABSTRACT

Candida auris is an and of a of C. auris .

After of a cluster of C. auris in the of an unit (ICU) of the United an package of of C. auris -

A of 70 were as being colonized with C. auris between February 2, 2015, and August 31, 2017; of , 66 (94%) had been admitted to the ICU before . Invasive C. auris -

The of C. auris was in the when there was in from a bundle of after removal of the . The were to from .

The of C. auris in was to be able to in the be by the for Unit in .
Candida auris is an invasive, multidrug-resistant fungus that has been widespread in healthcare settings, including intensive care units (ICUs) in the United States and Europe. Despite its emergence, the source of the pathogen remains unknown.

In Europe, Candida auris has been identified in the United Kingdom and Spain. In the United States, the first case was reported in April 2016 in the United Kingdom. A lookback exercise between February 2, 2015, and October 24, 2016, was undertaken to determine the source of the pathogen.

Methods

NHS Foundation

The study included patients admitted to the neurosciences ICU at Oxford University Hospitals NHS Foundation Trust identified 4 patients who were colonized with Candida auris. Of these 9 patients, 8 had been in the neurosciences ICU before diagnosis. All the isolates were from patients who were admitted to the ICU in South Korea in 2011.4

Methods

Candida auris was found to be positive. Isolates were identified with matrix-assisted laser desorption ionization–time of flight (MALDI-TOF), and antifungal susceptibility was determined by broth microdilution (see the Supplementary Appendix, available with the full text of this article at NEJM.org).
mitted to the neurosciences ICU before C. auris colonization or infection per patient were identified that is, who had been colonized or infected with C. auris who had never been colonized or infected with a clinical isolate). Controls were patients who had had no colonization or infection (i.e., a screening result). The electronic patient records of 9153 patients, representing 2872 unique samples, were obtained from patients, representing 2872 unique samples, from the first to last invasive isolate from that patient, with subsequent sterile blood cultures; the death was attributed to C. auris. One or more negative screening results were found in 838 patients (Fig. 1A). Of the 2872 patients, 267 (9.3%) were infected with more C. auris isolates in 62 patients (8%) who were colonized or infected with C. auris before diagnosis in this patient was made in 2015, which predated most cases. The median age was 52 years (interquartile range, 44 to 67) among the 361 and intracranial bleeding (Table S1 in the Supplementary Appendix).14

### RESULTS

A period was 2.9 cases per 100 neurosciences ICU patient-days of screening among 900 patients, with a median stay of 8.4 days in the ICU before diagnosis (interquartile range, 4.6 to 13.4). Other patients had been admitted to the neurosciences ICU before that patient had had a positive result. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients; 363 of whom had been admitted to the neurosciences ICU before the diagnosis. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients.

In multivariable models, the risk of colonization with C. auris was 2.9 cases per 100 neurosciences ICU patient-days of screening among 900 patients, with a median stay of 8.4 days in the ICU before diagnosis (interquartile range, 4.6 to 13.4). Other patients had been admitted to the neurosciences ICU before that patient had had a positive result. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients; 363 of whom had been admitted to the neurosciences ICU before the diagnosis. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients. The median age was 52 years (interquartile range, 44 to 67) among the 361 patients.

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A total of 128 environmental samples were obtained in February 2016, April 2017. C. auris was found in the general ward (66 of 73 [90%] isolates were resistant to fluconazole) and five additional cases were cultured — two from a patient hoist (S2 in the Supplementary Appendix). The risk of colonization was greatest in patients who had had exposure to the neurosciences ICU before diagnosis of colonization or infection. Although the risk of colonization was highest in those who had been in the general ward, it also increased in those who had been in the ICU before diagnosis of colonization (odds ratio, 6.80; 95% confidence interval, 2.96 to 15.63; P<0.001).

In the Supplementary Appendix, the risk of colonization was highest in patients who had been in the general ward (odds ratio, 7.8; 95% confidence interval, 1.64 to 45.2; P=0.01). The risk of colonization was also highest in patients who had been in the general ward and a patient hoist (odds ratio, 10.3; 95% CI, 1.64 to 65.2; P=0.01), followed by those who had been in the general ward and a patient hoist (odds ratio, 3.0; 95% CI, 1.0 to 9.2; P=0.07).

In Panel A, red indicates patients who had had exposure to the neurosciences ICU before diagnosis of colonization or infection, and green indicates patients who had had exposure to neither unit. The timing of the removal of reusable temperature probes is shown. The data in Panel B are deduplicated to unique patient screening days — that is, in instances in which multiple samples were obtained from a patient on the same day, this is represented as a single line. In Panel B, the data are represented as a rate of new cases detected per week, where a rate of 1 is shown as a line with an error bar that is, in instances in which multiple samples were obtained from a patient on the same day, this is represented as a single line. In Panel B, the data are represented as a rate of new cases detected per week, where a rate of 1 is shown as a line with an error bar.

**Antifungal Susceptibility Testing**

The 66 isolates from the ICU were all susceptible to azole, and 66 of 73 (90%) and 67 of 73 (91%) were susceptible to amphotericin B, respectively. The isolates were resistant to fluconazole, itraconazole, and voriconazole.

**Figure 1. Detection of C. auris and Rates of Screening.**

In Panel A, red indicates patients who had had exposure to the neurosciences ICU before diagnosis of colonization or infection, and green indicates patients who had had exposure to neither unit. The timing of the removal of reusable temperature probes is shown. The data in Panel B are deduplicated to unique patient screening days — that is, in instances in which multiple samples were obtained from a patient on the same day, this is represented as a single line. In Panel B, the data are represented as a rate of new cases detected per week, where a rate of 1 is shown as a line with an error bar that is, in instances in which multiple samples were obtained from a patient on the same day, this is represented as a single line. In Panel B, the data are represented as a rate of new cases detected per week, where a rate of 1 is shown as a line with an error bar.
### Table 1. Multivariable Predictors of *Candida auris* Colonization.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (N = 361)</th>
<th>Case Patients (N = 66)</th>
<th>Univariable Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio (95% CI)</td>
<td>P Value</td>
<td>Odds Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>Median ICU stay before diagnosis (IQR) —</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>days†</td>
<td>1.8 (0.7–6.6)</td>
<td>8.4 (4.6–13.4)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Length of ICU stay before diagnosis</strong></td>
<td>Reference</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>3.89 (2.38–6.36)</td>
<td>2.24 (1.30–3.86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 days</td>
<td>7.37 (3.65–14.89)</td>
<td>2.97 (1.35–6.53)</td>
<td></td>
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</tr>
<tr>
<td>5 days</td>
<td>12.68 (5.38–29.88)</td>
<td>2.78 (1.02–7.54)</td>
<td></td>
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<tr>
<td>10 days</td>
<td>6.75 (2.78–16.40)</td>
<td>0.69 (0.22–2.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Axillary temperature monitoring — no. (%)</strong></td>
<td>122 (34)</td>
<td>57 (86)</td>
<td>12.41 (5.94–25.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Median blood sodium level (IQR) — mmol/liter</strong></td>
<td>139.3 (137.1–141.1)</td>
<td>141.4 (138.5–143.6)</td>
<td>1.20 (1.09–1.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Median neutrophil count (IQR) — cells/mm³†</strong></td>
<td>8600 (6600–10,900)</td>
<td>9600 (7300–10,900)</td>
<td>1.17 (0.37–3.71)</td>
<td>1.69 (0.45–6.42)</td>
</tr>
<tr>
<td><strong>Neutrophil count</strong></td>
<td>4000 cells/mm³</td>
<td>Reference</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>7000 cells/mm³</td>
<td>2.18 (1.40–3.41)</td>
<td>2.21 (1.30–3.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10,000 cells/mm³</td>
<td>4.41 (1.84–10.59)</td>
<td>4.72 (1.64–13.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15,000 cells/mm³</td>
<td>1.17 (0.37–3.71)</td>
<td>1.69 (0.45–6.42)</td>
<td></td>
</tr>
<tr>
<td><strong>Median body temperature (IQR) — °C</strong></td>
<td>36.5 (36.3–36.9)</td>
<td>36.9 (36.6–37.3)</td>
<td>2.44 (1.78–3.35)‡‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Any antifungal treatment — no. (%)§</strong></td>
<td>3 (1)</td>
<td>3 (5)</td>
<td>5.68 (1.12–28.79)‡‡</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Complete data were available for all factors shown for all 66 case patients and 361 controls. Only factors in the multivariable model are shown; more complete information about the characteristics of case patients and controls, as well as the univariable odds ratios for all factors, including sex, age, primary diagnosis, emergency admission status, invasive ventilation, central venous access, albumin level, potassium level, creatinine level, hemoglobin level, heart rate, respiratory rate, blood pressure, and use of broad-spectrum antibiotics, are provided in Table S1 in the Supplementary Appendix. CI denotes confidence interval, ICU intensive care unit, and IQR interquartile range.

†There was a nonlinear relationship between risk of colonization and duration of stay in the neurosciences ICU and between risk of colonization and neutrophil count (details are provided in Table S1 in the Supplementary Appendix).

‡The odds ratio per 0.5°C increase in body temperature is shown.

§All the patients who had received treatment with an antifungal agent received fluconazole only.
The duration of colonization among patients for whom vital status was ascertainable, 90-day mortality was 20% (13 of 64) and 207 (16%), 66 of 207 (32%), and 107 of 207 (52%), respectively (P<0.001).

A total of 60 case patients (58 colonized and 2 were culture-negative) had a total of 914 screening results found to be positive according to the number of days since their first positive screening result, with death without clearance treated as a competing risk. Because a single screen was imperfectly sensitive, clearance of colonization was defined as two consecutive negative screening results, timed from the day of the first positive result. A graph constructed under an alternative definition of three consecutive negative screening results is provided in Figure S5 in the Supplementary Appendix. Of the 11 patients whose colonization was cleared according to this definition, 2 had a relapse. Panel B shows the proportion of next screening results found to be positive according to the number of consecutive negative screening results, by number of previous positive results. The crude mortality rate was similar among case patients, the first positive screening result was from the axilla in 22 of 60 patients (37%), from one or both axillae in 44 of 60 (73%), and from other sites in 24 of 60 (40%). No micafungin or flucytosine resistance was observed. No C. auris isolate was amphotericin-resistant. No C. auris isolate was fluconazole-resistant. No C. auris isolate was echinocandin-resistant. No C. auris isolate was tericin-resistant. No C. auris isolate was teicoplanin-resistant. No C. auris isolate was flucytosine-resistant. No C. auris isolate was fluconazole-resistant. No C. auris isolate was echinocandin-resistant. No C. auris isolate was tericin-resistant. No C. auris isolate was amphotericin-resistant. No C. auris isolate was fluconazole-resistant. No C. auris isolate was echinocandin-resistant. No C. auris isolate was micafungin-resistant. No C. auris isolate was flucytosine-resistant. No C. auris isolate was fluconazole-resistant. No C. auris isolate was echinocandin-resistant. No C. auris isolate was micafungin-resistant. No C. auris isolate was flucytosine-resistant. No C. auris isolate was fluconazole-resistant. No C. auris isolate was echinocandin-resistant. No C. auris isolate was micafungin-resistant. No C. auris isolate was flucytosine-resistant.
We report an outbreak of *C. auris* in our neurosciences intensive care unit (ICU). The rate of *C. auris* evolution was 5.75 mutations per genome per year (95% highest posterior density interval, 4.49 to 7.11) (Fig. S7 in the Supplementary Appendix). The rate of evolution within the African *C. auris* clade (Fig. 3) was likely to have resulted from simultaneous acquisition of multiple strains or from serial acquisition of different genotypes. The clade (Fig. S9 in the Supplementary Appendix) formed a single subclade, estimated to have emerged in April 2013 (95% highest posterior density interval, 2012 to 2013). The clade was 40 SNPs (P = 0.62 by rank-sum test) that differed from the Indian clade by at most 1 SNP. We could not find the clades in any patient samples; for example, Patient 2 had a subclade of strains with closely genetically related sequences that differed from each other by more than 5 SNPs (P = 0.34 for trend). There was no evidence that patients 24 and 32 had mixed colonization similar to that found on Temperature Probes 1 and 2. Conversely, transmission between patients in nearby beds was to be in the ICU, with 9 of 35 (26%) at any subsequent time point. There was no evidence that patients were in the ICU, as compared with 9 of 35 (26%) at any subsequent time point. There was no evidence that patients were in the ICU, as compared with 9 of 35 (26%) at any subsequent time point.

**DISCUSSION**

The rate of *C. auris* evolution was likely to have resulted from simultaneous acquisition of multiple strains or from serial acquisition of different genotypes. The clade (Fig. S9 in the Supplementary Appendix) formed a single subclade, estimated to have emerged in April 2013 (95% highest posterior density interval, 2012 to 2013). The clade was 40 SNPs (P = 0.62 by rank-sum test) that differed from the Indian clade by at most 1 SNP. We could not find the clades in any patient samples; for example, Patient 2 had a subclade of strains with closely genetically related sequences that differed from each other by more than 5 SNPs (P = 0.34 for trend). There was no evidence that patients 24 and 32 had mixed colonization similar to that found on Temperature Probes 1 and 2. Conversely, transmission between patients in nearby beds was to be in the ICU, with 9 of 35 (26%) at any subsequent time point. There was no evidence that patients were in the ICU, as compared with 9 of 35 (26%) at any subsequent time point. There was no evidence that patients were in the ICU, as compared with 9 of 35 (26%) at any subsequent time point.

**Figure 3.** Maximum-Likelihood Phylogeny Comparing 20,000 SNPs of *C. auris* isolates from India, the United States, and South Africa with four additional Indian isolates. Shown are 78 outbreak sequences as compared with 140 sequences from isolates obtained from reusable devices for use (see the Supplementary Appendix).
Candida auris Outbreak in an Intensive Care Setting

Temperatures probes are difficult to clean with wipes, with a two-layer rubber sheath protecting the distal end of the wire adjacent to the sensor (Fig. S3 in the Supplementary Appendix). In addition, a recent study has shown that quaternary ammonium compounds have relatively poor activity against all candida species.17

Several lines of evidence support the role of these temperature probes in the transmission of C. auris. Controlling for length of stay in the neurosciences intensive care unit (ICU), beds are arranged in a circular layout, such that bed 1 is adjacent to beds 16 and 2, bed 2 is adjacent to beds 1 and 3, and so on. Beds 1 through 13 are in an open-plan configuration, and beds 14 through 16 are in separate side rooms. NA denotes not applicable.

The New England Journal of Medicine
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Neurosciences ICU, vital signs, temperature probe.

Previous to C. auris colonization in the ICU, there was 90% mortality in patients with C. auris colonized in the ICU. In 2016, there were 30% mortality in patients with C. auris colonized in the ICU. However, invasive infections did not develop in patients with C. auris colonized in the ICU.

C. auris was not completely eliminated, and cases continued to occur in patients admitted to the ICU. Antifungal agents have been used to decolonize patients, and with 2% chlorhexidine washcloths, the duration of colonization was minimized. There were no invasive infections after November 2016; however, despite the use of single-dose micafungin prophylaxis for surgical procedures in colonized patients, the 90-day crude mortality associated with colonization of patients testing positive after three negative results, and previous use of antifungal agents, the odds of infection of C. auris infection were 5% of C. auris cases had been C. albicans to C. auris. In a study that followed the number of C. auris infections, the probability of C. auris infection in the hospital environment, particularly in the ICU, was higher than in previous studies. This may reflect the survival of this organism in the hospital environment, particularly C. auris.

Antifungal susceptibility testing revealed resistance to fluconazole and other antifungal agents. The use of fluconazole was also a strong risk factor, and the 2% of case patients had been exposed. Antifungal agents have previously been reported to increase the risk of infection in patients with C. auris. Colonization or infection by a C. auris species from our isolate was not completely eliminated, and cases continued to occur in patients admitted to the ICU. Our results indicate that reusable prophylaxis for surgical procedures in colonized patients is necessary, and the use of single-dose micafungin prophylaxis for surgical procedures in colonized patients is effective in preventing invasive infections.

On the basis of the analysis of repeated screening of patients, the percentage of patients with C. auris within a hospital was more than 2%. In a study of patients with C. auris, the percentage of patients with C. auris was 78%. Specific targeted interventions were used to decolonize patients; however, these interventions were routine, and cold weather probes were used to monitor temperature probes. The duration of colonization was approximately 2 to 3 days, with 2% of patients having a temperature below 37.5°C. The frequency of patients with C. auris was 1 to 3%.

In conclusion, on the basis of our investigation of seven C. auris isolates in the United Kingdom, the percentage of patients with C. auris was increased. The frequency of patients with C. auris was 1 to 3%.

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Candida auris hospital-acquired multidrug-resistant fungemia caused by
S. et al. Simultaneous emergence of multidrug-resistant species in the UK: first four reported cases in
15. Eyre DW, Cule ML, Griffiths D, et al. First case of Candida auris from bacte-

The full text of this article is available at NEJM.org.
Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.
The online version of this article includes supplementary material.

Dr. Eyre is an NIHR Clinical Lecturer and Robertson Foundation Investigator. Drs. Petro Crook are NIHR HPRU: John Coia, Neil French, Charis Marwick, Mike Sharland.