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# *Candida auris* candidaemia in Indian ICUs: analysis of risk factors

**Shivaprakash M. Rudramurthy[1], Arunaloke Chakrabarti[1]*, Raees A. Paul[1], Prashant Sood[1]†, Harsimran Kaur[1], Malini R. Capoor[2], Anupma J. Kindo[3], Rungmei S. K. Marak[4], Anita Arora[5], Raman Sardana[6], Shukla Das[7], Deepinder Chhina[8], Atul Patel[9], Immaculata Xess[10], Bansidhar Tarai[11], Pankaj Singh[1] and Anup Ghosh[1]**

*[1]Postgraduate Institute of Medical Education and Research, Chandigarh, India; [2]Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India; [3]Sri Ramachandra Medical College and Research Institute, Chennai, India; [4]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; [5]Fortis Escorts Heart Institute, New Delhi, India; [6]Indraprastha Apollo, New Delhi, India; [7]University College of Medical Sciences, University of Delhi, New Delhi, India; [8]Dayanand Medical College and Hospital, Ludhiana, India; [9]ID Clinic and Sterling Hospital, Ahmedabad, India; [10]All India Institute of Medical Sciences, New Delhi, India; [11]Max Hospital, New Delhi, India*

*Corresponding author. Department of Medical Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. Tel: +91-172-2755173; Fax: +91-172-2744401; E-mail: arunaloke@hotmail.com
†Present address: University of Aberdeen, Aberdeen, UK.

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**Objectives:** To identify the risk factors associated with *Candida auris* candidaemia, as this fungus now poses a global threat.

**Methods:** We performed a subgroup analysis of a previously reported study of 27 Indian ICUs. The clinical data of candidaemia cases due to *C. auris* and other *Candida* species were compared to determine significant risk factors associated with *C. auris* infection.

**Results:** Of the 1400 candidaemia cases reported earlier, 74 (5.3%) from 19 of 27 ICUs were due to *C. auris*. The duration of ICU stay prior to candidaemia diagnosis was significantly longer in patients with *C. auris* candidaemia (median 25, IQR 12–45 days) compared with the non-*auris* group (median 15, IQR 9–28, $P < 0.001$). Based on logistic regression modelling, admission to north Indian ICUs [OR 2.1 (1.2–3.8); $P = 0.012$], public-sector hospital [OR 2.2 (1.2–3.9); $P = 0.006$], underlying respiratory illness [OR 2.1 (1.3–3.6); $P = 0.002$], vascular surgery [OR 2.3 (1.00–5.36); $P = 0.048$], prior antifungal exposure [OR 2.8 (1.6–4.8); $P < 0.001$] and low APACHE II score [OR 0.8 (0.8–0.9); $P = 0.007$] were significantly associated with *C. auris* candidaemia. The majority (45/51, 88.2%) of the isolates were clonal. A considerable number of isolates were resistant to fluconazole ($n = 43$, 58.1%), amphotericin B ($n = 10$, 13.5%) and caspofungin ($n = 7$, 9.5%).

**Conclusions:** Although *C. auris* infection has been observed across India, the number of cases is higher in public-sector hospitals in the north of the country. Longer stay in ICU, underlying respiratory illness, vascular surgery, medical intervention and antifungal exposure are the major risk factors for acquiring *C. auris* infection even among patients showing lower levels of morbidity.

## Introduction

Infection due to *Candida auris* has emerged as an important challenge in the management of patients admitted to ICUs in India due to its outbreak potential, multidrug resistance and associated high mortality. Since the first report of ear-canal infection by *C. auris* in Japan in 2009,[1] candidaemia due to this yeast has been reported from three continents with a large number of cases from India having been noted.[2–13] The phenotypic and genotypic characteristics of the isolates from India,[2,3] Kuwait[4] and South Africa[5] were similar and differed from those of Japanese[1] and Korean[6,7] isolates. Within India, the isolates were clonal in origin, even among hospitals located far apart.[3] These Indian isolates had reduced susceptibility to antifungals, particularly triazoles. To identify the infection early, it is important to study the risk factors associated with *C. auris* candidaemia as opposed to other *Candida* species. We were in the unique position of possessing detailed clinical data and the isolates of 1400 candidaemia cases from a prospective study conducted over 27 ICUs across India.[10] The present study was a subgroup analysis and comparison of the clinical details of *C. auris* and non-*auris* candidaemia cases to identify the risks associated with *C. auris* candidaemia.

## Materials and methods

### Study design, settings and definitions

Previously reported clinical data from ICU-acquired candidaemia cases identified between April 2011 and September 2012 in 27 medical and surgical ICUs across India were retrieved.[10] A case of ICU-acquired candidaemia was defined as the isolation of *Candida* species from blood cultures obtained >48 h after ICU admission or < 48 h after discharge from an ICU. Patients already diagnosed with candidaemia before ICU admission or those transferred from another ICU with a positive culture for any yeast infection were excluded from the study. Prior antifungal exposure was defined as empirical or prophylactic therapy with antifungals within 30 days prior to the diagnosis of candidaemia. Outcome was determined 30 days after onset of candidaemia and cure was considered complete microbiological resolution. A death attributed to candidaemia was ascertained by the treating physician independently on the basis of clinical judgement and microbiology reports. The detailed study design, definition and data collection were described in our earlier report.[10] Both adult and paediatric cases were included in the present study. The phenotypic and molecular characterizations were performed at the national reference centre (Postgraduate Institute of Medical Education and Research, Chandigarh, India).

### Ethics

The study was cleared by the respective ethics committees of the participating centres.

### Microbiology

The isolates were phenotypically characterized based on morphology on corn meal agar (CMA), growth at different temperatures (37, 40, 42 and 45 °C) and in the presence of 0.01% or 0.1% cycloheximide, assimilation of a panel of 14 sugars, and fermentation of D-glucose, D-maltose, sucrose and L-lactose. The identity of all *C. auris* isolates was confirmed by sequencing the internal transcribed spacer (ITS) region and the D1/D2 region of the large subunit (28S) of the ribosomal DNA.[14] Molecular typing of isolates ($n = 51$) was performed by amplified fragment length polymorphism (AFLP) according to our earlier protocol with minor modifications (see Supplementary methods available as Supplementary data at *JAC* Online).[15] Antifungal susceptibility testing of *C. auris* isolates with amphotericin B, fluconazole, voriconazole, itraconazole, posaconazole, caspofungin, anidulafungin and micafungin was performed by broth microdilution using the CLSI M27-A3 guidelines.[16] As the breakpoints for *C. auris* were not defined, the breakpoints suggested for yeast in CLSI M27-S3 were used to interpret the MICs for this new yeast, and for other *Candida* species CLSI M27-S4 was followed.[17] For amphotericin B, MIC > 1 mg/L was considered resistant. Multidrug resistance was defined as resistance to two or more classes of antifungals.

### Comparison of *C. auris* and non-*auris* candidaemia cases

The demographic and clinical data of patients with *C. auris* and non-*auris* candidaemia cases were compared. Separately, data of *C. auris* were compared with five major isolated species, namely *Candida albicans*, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis* and *Candida krusei*.

### Statistical analysis

While comparing *C. auris* and non-*auris* candidaemia cases, continuous variables were expressed as mean or medians and IQRs whereas categorical variables were described as frequencies and percentages. To identify the clinical variables among those groups, univariate analysis was conducted by Pearson's $\chi^2$ test and Fisher's exact test to compare categorical variables; Student's *t*-test and the Mann–Whitney *U*-test were employed for continuous data. The independent effects of the variables on *C. auris* candidaemia were determined using a multivariate model. All variables with $P < 0.1$ in the bivariate analyses were included into the multivariate analyses. Multivariate logistic regression was conducted in step-by-step forward mode adjusted to the Wald statistic. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated for each variable. Model fitness was evaluated by the Hosmer–Lemeshow goodness of fit and the area under the receiving operating characteristic (ROC) curve. The effect size was measured by the Nagelkerke $R^2$ coefficient. Data were analysed using SPSS statistical software, version 22.0 (IBM, Chicago, IL).

## Results

### Clinical and demographic details of *C. auris* candidaemia cases

During the study period 1400 patients were diagnosed with ICU-acquired candidaemia, of which 5.3% (74 patients) were due to *C. auris*. The majority (52, 70.3%) of these *C. auris* cases were adult patients. *C. auris* candidaemia was identified in 19 of 27 ICUs across India, more frequently from ICUs in the north of the country ($n = 54$, 73% and 10 of 11 ICUs) as compared with other regions ($n = 20$, 27%; $P < 0.001$). Nine cases of *C. auris* candidaemia were diagnosed at four ICUs in south India, seven at three ICUs in east India and four at two ICUs in west India. Of the 11 public-sector hospitals (north, 6; south, 3; west, 1; east, 1) and 16 private-sector hospitals (north, 5; south, 6; east, 2; west, 3), isolation of *C. auris* was significantly higher in public-sector hospitals compared with private-sector hospitals (46, 62.2% versus 28, 37.8%, $P < 0.001$). Demographically the patients included 46 (62.2%) males and 28 (37.8%) females; median age 39 years (IQR 16–58.5). Among the 22 children, 6 were neonates (4 were premature), and 6 were infants. Underlying co-morbid illness included pulmonary ($n = 30$, 40.5%), renal ($n = 16$, 21.6%), cardiovascular ($n = 15$, 20.3%), gastrointestinal ($n = 7$, 9.5%) and liver ($n = 5$, 6.8%) diseases. Among underlying respiratory illness, pneumonia was the common presentation ($n = 11$, 36.7%) followed by chronic obstructive pulmonary disease ($n = 3$, 10.0%) and acute respiratory distress syndrome ($n = 3$, 10.0%). Neutropenia was noted in two (2.7%), malignancy in six (8.1%) and other immune-deficient conditions in four (5.4%) patients. The mean APACHE II score at admission was $14.2 \pm 5.17$ in those patients. A sizeable number of *C. auris* patients received medical intervention in the ICU including urinary catheterization ($n = 56$, 75.7%), central venous catheterization ($n = 53$, 71.6%), post-operative drainage catheter ($n = 25$, 33.8%) and total parenteral nutrition ($n = 15$, 20.3%). Outcome of antifungal treatment could be evaluated in 48 (64.9%) patients. The majority of those patients [32 (66.6%)] received azoles, including fluconazole in 27 (56.2%) patients; amphotericin B deoxycholate was prescribed in 11 (22.9%) and echinocandins in 5 (10.4%) patients. The all-cause 30 day crude and attributable mortality in *C. auris* candidaemia patients were 41.9% and 27%, respectively, whereas the crude and attributable mortality for *C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. krusei* and *C. glabrata* were 35.4% and 24.5%, 37.5% and 25.6%, 31.9% and 18.4%, 23.7% and 10.5%, and 43.2% and 24.3%, respectively.

### *Comparison of C. auris and non-auris candidaemia cases*

Comparisons by bivariate analyses of *C. auris* with non-*auris* (together), *C. tropicalis*, *C. albicans*, *C. parapsilosis*, *C. krusei* and *C. glabrata* individually are provided in Table 1 and Tables S1–S6, respectively. The duration of ICU stay prior to candidaemia diagnosis was significantly longer in *C. auris* candidaemia (median 25, IQR 12–45 days) compared with non-*auris* patients (median 15, IQR 9–28, $P < 0.001$) together and also when compared individually with *C. tropicalis* (median 14, IQR 8–28 days, $P < 0.001$), *C. albicans* (median 14, IQR 8–28 days, $P < 0.001$), *C. glabrata* (median 16.5, IQR 9–34.7 days, $P = 0.028$), *C. parapsilosis* (median 18, IQR 12–33 days, $P = 0.041$) and *C. krusei* (median 11, IQR 8–17.7 days, $P < 0.001$) candidaemia cases. Compared with *C. albicans* and *C. tropicalis* candidaemia, patients with *C. auris* infection had significantly higher antifungal exposure prior to candidaemia diagnosis, and the majority were treated with fluconazole (15/23, 65.2%; median duration 7 days, IQR 4.25–21.25 days), followed by an echinocandin (30.4%; caspofungin 6/23, median duration 3 days, IQR 1.5–12.5 days; anidulafungin 1/23). The presence of a central venous line was not significantly associated with *C. auris* candidaemia cases (65% versus 71%, $P = 0.152$). However, the duration of central line in days was significantly higher in *C. auris*-infected patients compared with non-*auris* candidaemia patients (median 10.5, IQR 5–27 days versus median 8, IQR 4–14 days, $P = 0.018$). Total parenteral nutrition (TPN) was significantly associated with *C. auris* candidaemia compared with non-*auris* candidaemia patients (20.3% versus 12.1% $P = 0.036$). On multivariate logistic regression analysis, admission to north India ICUs ($P = 0.012$) and public-sector hospital ($P = 0.006$), underlying respiratory illness ($P = 0.002$), vascular surgery ($P = 0.048$), prior antifungal exposure ($P < 0.001$) and low APACHE II score ($P = 0.007$) were significantly associated with *C. auris* infection compared with five other non-*auris* candidaemia cases (Table 2).

### *Identification, typing and antifungal susceptibility testing of C. auris isolates*

*C. auris* could grow at 42 °C, but failed to grow in the presence of 0.01% or 0.1% cycloheximide. The isolates could ferment maltose. The sequencing of the ITS and D1/D2 regions of the 28S subunit of ribosome revealed 99%–100% homology with *C. auris*; >99% homology with an unrelated *C. auris* strain (HE797774.1) and an earlier reported isolate from New Delhi (KC692063.1), and 100% homology with Korean ear isolates (EU881961.1). AFLP results showed that the majority of the *C. auris* isolates (45/51, 88.23%) had an identical (99%–100%) fingerprint, suggesting the clonal nature of the isolates. Six isolates (11.8%) clustered separately from the main clone and varied between 3% and 10.6% (Figure 1).

The results of *in vitro* antifungal susceptibility testing of *C. auris* isolates are presented in Table 3. Antifungal resistance was noted to amphotericin B ($n = 10$, 13.5%), fluconazole ($n = 43$, 58.1%), voriconazole ($n = 2$, 2.7%), itraconazole ($n = 3$, 4.3%) and caspofungin ($n = 7$, 9.5%). Multidrug resistance was noted in 12 (16.2%) isolates, of which 11 (91.7%) showed resistance across two antifungal classes and one isolate showed resistance across three antifungal classes (polyene, azoles, echinocandins).

## Discussion

The present study depicts the prevalence, patient characteristics and risk factors of a large number ($n = 74$) of *C. auris* candidaemia cases in ICUs across India. The yeast was isolated from 19 of 27 ICUs. The comparison between patient details of *C. auris* and non-*auris* candidaemia indicated the association of *C. auris* with five independent risk factors namely admission to ICUs of north Indian hospitals, admission to public-sector hospitals, namely respiratory disease, vascular surgery and prior antifungal exposure even in patients with a low APACHE II score at admission. However, variation was noted in the number of those risk factors when *C. auris* was compared with five other *Candida* species individually.

In earlier studies, with small numbers of cases in undefined populations, the prevalence of *C. auris* candidaemia was reported to be 0.04% in the UK[9] and 30% in India.[2] The present study dealt with the largest number of *C. auris* candidaemia cases yet examined. The prevalence of 5.3% in our study is, therefore, a more accurate estimation and ranks *C. auris* fifth among all candidaemia cases in Indian ICUs.[10] The infection was first noted in Delhi,[18] and then spread across the country, though higher prevalence was noted in north Indian public-sector hospitals. It was difficult to identify the reason for the higher prevalence of *C. auris* candidaemia in north India from the present study, as the report was only a subgroup analysis of a prior study and data on infection control practices or other possible reasons for higher rates of candidaemia in ICUs were not captured. From north India, five private-sector and four public-sector hospitals were included in the study. The overcrowding of patients in public-sector hospitals due to healthcare cost constraints, and possible compromise in infection control practices in those hospitals, may be responsible for the higher rate of *C. auris* candidaemia.

*C. auris* candidaemia was diagnosed even in patients exhibiting lower morbidity (APACHE II score $14.29 \pm 5.18$), though *C. auris* was not recognized as a highly virulent organism compared with *C. albicans* and *C. tropicalis* in a recent study.[19] Hyphal filamentation, a possible major virulence factor in pathogenic *Candida* species, is also absent in *C. auris*. The presence of *C. auris* candidaemia in lower-morbidity patients may be due to multiple medical interventions in those patients during their ICU stay. TPN, urinary catheterization, post-operative drain placement and vascular surgery were significant variables associated with *C. auris* candidaemia in the present study. In a recent outbreak of 18 cases of *C. auris* in critically ill patients admitted to an ICU, all of them had been exposed to antibiotics and a considerable number to multiple invasive procedures such as central venous catheterization (100%) and surgery (55.6%) before acquisition of *C. auris* infection.[20] The significant association of longer duration of central venous lines, urinary catheterization, post-operative drainage in our patients, and the relatively late acquisition of infection after ICU admission support the hypothesis of nosocomial transmission of *C. auris* in ICUs. However, a systematic prospective multicentre study is required to identify the source of the agent in the hospital and elucidate the transmission mechanism. Earlier reports noted urinary catheterization in 83%–91.6% of cases,[2,3,11] central venous catheterization in 42%–94%,[2,3,11] broad-spectrum antibiotic use in 75%–100%,[3,4] total parenteral nutrition in 47%–100%,[2,7,11] longer ICU stay in 58%–91.6%[2,3] and surgery in the last 30 days in 58.3%–66.6%[2,7] for patients with *C. auris* candidaemia. However,

**Table 1.** Univariate analysis of clinical variables of *C. auris* and non-*auris* candidaemia cases

| Variables | *C. auris* | Non-*auris* | *C. tropicalis* | *C. albicans* | *C. parapsilosis* | *C. krusei* | *C. glabrata* |
|---|---|---|---|---|---|---|---|
| Number of cases (%) | 74 (6.4) | 1087 (93.6) | 503 (43.3) | 293 (25.2) | 141 (12.1) | 76 (6.5) | 74 (6.4) |
| Median age in years (IQR) | 39 (16–58.5) | – | 38 (20–60) | 35 (1–58) | 34 (14–55) | 0.05 (0.02–4.4) | 49.5 (30–66) |
| Male, *n* (%) | 46 (62.2) | – | 304 (60.4) | 185 (63.1) | 84 (59.6) | 54 (71.1) | 34 (45.9) |
| Public-sector hospital, *n* (%) | 29 (39.2) | 441 (40.6) | 200 (39.8) | 33 (11.3) | 56 (39.7) | 21 (27.6) | 46 (62.2) |
| OR (95% CI) | – | 2.4 (1.4–3.9) | 2.4 (1.5–4.1) | 1.9 (11–3.2) | 2.4 (1.3–4.4) | 4.3 (2.8–8.5) | 2.5 (1.3–4.9) |
| *P* value | – | <0.001 | <0.001 | <0.001 | 0.001 | <0.001 | 0.004 |
| Northern India ICU, *n* (%) | 54 (73) | 502 (46.2) | 245 (48.7) | 145 (49.5) | 58 (41.1) | 18 (23.7) | 36 (48.6) |
| OR (95% CI) | – | 3.1 (1.8–5.3) | 2.8 (1.6–4.8) | 2.7 (1.5–4.8) | 3.8 (2.2–7.1) | 8.7 (4.1–18.1) | 2.8 (1.4–5.6) |
| *P* value | – | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.002 |
| APACHE II at admission, mean ± SD | 14.2 ± 5.17 | 17 ± 6.01 | 17.4 ± 5.69 | 17.9 ± 6.42 | 16 ± 7.0 | 18 ± 6.71 | 16.5 ± 5.31 |
| *P* value | | 0.002 | 0.002 | 0.002 | 0.089 | 0.089 | 0.045 |
| Central venous catheterization, *n* (%) | 53 (71.6) | | – | – | – | 31 (40.8) | – |
| OR (95% CI) | | | – | – | – | 3.6 (1.8–7.2) | – |
| *P* value | | | – | – | – | <0.001 | |
| Urinary catheterization, *n* (%) | 56 (75.5) | 670 (61.6) | 335 (66.6) | 167 (57) | 92 (65.2) | 21 (27.6) | – |
| OR (95% CI) | | 1.9 (1.1–3.1) | 1.5 (0.8–2.7) | 2.3 (1.3–4.1) | 1.6 (0.8–3.1) | 8.1 (3.5–16.9) | – |
| *P* value | | 0.01 | 0.075 | 0.002 | 0.078 | <0.001 | – |
| Drainage catheterization, *n* (%) | 25 (33.8) | 249 (22.9) | 123 (24.5) | 60 (20.5) | 32 (22.7) | 9 (11.8) | – |
| OR (95% CI) | | 1.79 (1–2.8) | 1.5 (0.9–2.6) | 1.9 (1.1–3.4) | 1.7 (0.9–3.2) | 3.7 (1.6–8.8) | – |
| *P* value | | 0.026 | 0.06 | 0.013 | 0.057 | 0.001 | – |
| Total CVL median days (IQR) | 10 (7–25) | 8 (6–22) | 11 (6–20) | 12 (6–23.7) | – | 7.5 (5–14.2) | |
| *P* value | | 0.007 | 0.003 | 0.013 | – | <0.001 | |
| Vascular surgery, *n* (%) | 8 (10.8) | 51 (4.7) | 22 (4.4) | – | – | – | – |
| OR (95% CI) | | 2.4 (1.1–5.4) | 2.6 (1.1–6.1) | – | – | – | – |
| *P* value | | 0.029 | 0.028 | – | – | – | – |
| ICU DOA to DOPC median days (IQR) | 10 (4.7–22.2) | 7 (3–13) | 7 (3–13) | 7 (3.5–14) | – | 5 (3–8) | 6.5 (3–13.2) |
| *P* value | | 0.13 | 0.014 | 0.014 | – | <0.001 | 0.027 |
| CVL insertion to DOPC, median days (IQR) | 10.5 (5–27) | 8 (4–14) | 7 (4–13) | 7.5 (4–14.5) | – | 4 (3–7) | 7 (3–15) |
| *P* value | | 0.018 | 0.010 | 0.010 | – | 0.001 | 0.080 |
| Previous antifungal exposure, *n* (%) | 23 (31.1) | 159 (14.6) | 66 (13.1) | 33 (11.3) | 28 (19.9) | – | – |
| OR (95% CI) | | 2.6 (1.5–4.4) | 2.9 (1.7–5.2) | 3.5 (1.9–6.5) | 1.8 (0.9–3.4) | – | – |
| *P* value | | <0.001 | <0.001 | <0.001 | 0.049 | – | – |
| Previous fluconazole exposure, *n* (%) | 15 (20.3) | 132 (12.1) | 55 (10.9) | 28 (9.6) | – | – | – |
| OR (95% CI) | | 1.8 (1–3.3) | 2 (1.1–3.8) | 2.4 (1.2–4.7) | – | – | – |
| *P* value | | 0.038 | 0.022 | 0.012 | – | – | – |
| Previous echinocandin exposure, *n* (%) | 7[a] (9.5) | 9 (0.8) | 4 (0.8) | 2 (0.7) | 1 (0.7) | – | – |
| OR (95% CI) | | 12.5 (4.5–34.6) | 13 (3.7–45.7) | 15.2 (3–74.8) | 14.6 (1.7–121.3) | – | – |
| *P* value | | <0.001 | <0.001 | <0.001 | 0.003 | – | – |

OR, odds ratio; CVL, central venous line; DOA, date of admission; DOPC, date of positive candidaemia.
[a]The majority (6/7) were exposed to caspofungin and only one patient received anidulafungin.

no statistical correlation was attempted in those studies, possibly due to the small number of patients studied.

The incidence of *C. auris* candidaemia was significantly higher in patients who had previous exposure to fluconazole or echinocandin compared with that in patients with susceptible species such as *C. albicans* and *C. tropicalis*. The difference was not significant with relatively resistant species such as *C. krusei*, *C. glabrata* and *C. parapsilosis*. These findings suggest that

**Table 2.** Multivariate analysis of *C. auris* and non-*auris* candidaemia cases

| Variables | OR (95% CI) | *P* value |
|---|---|---|
| *C. auris* and non-*C. auris* (model = AUC: 75.5%, accuracy: 93.6%, $R^2 = 0.137$, $P < 0.001$) | | |
| public-sector hospital | 2.2 (1.25–3.87) | 0.006 |
| northern India ICUs | 2.1 (1.17–3.84) | 0.012 |
| underlying respiratory disease | 2.1 (1.31–3.60) | 0.002 |
| urinary catheter | 1.9 (1.11–3.42) | 0.02 |
| vascular surgery | 2.3 (1.00–5.36) | 0.048 |
| prior antifungal exposure | 2.8 (1.64–4.86) | <0.001 |
| APACHE II at admission | 0.8 (0.81–0.96) | 0.007 |
| *C. auris* and *C. tropicalis* (model = AUC: 74.1%, accuracy: 87.7%, $R^2 = 0.165$, $P < 0.001$) | | |
| public-sector hospital | 2.2 (1.25–4.07) | 0.006 |
| northern India ICUs | 2.0 (1.09–3.73) | 0.025 |
| prior antifungal exposure | 3.5 (1.95–6.52) | <0.001 |
| APACHE II at admission | 0.8 (0.81–0.96) | 0.007 |
| *C. auris* and *C. albicans* (model = AUC: 75.3%, accuracy: 79.8%, $R^2 = 0.188$, $P < 0.001$) | | |
| public-sector hospital | 2.7 (1.56–4.95) | 0.001 |
| underlying respiratory disease | 2.1 (1.18–3.79) | 0.011 |
| prior antifungal exposure | 3.3 (1.71–6.43) | <0.001 |
| urinary catheter | 2.3 (1.27–4.33) | 0.006 |
| APACHE II at admission | 0.8 (0.82–0.97) | 0.009 |
| *C. auris* and *C. parapsilosis* (model = AUC: 69.5%, accuracy: 69.3%, $R^2 = 0.153$, $P < 0.001$) | | |
| northern India ICU | 3.9 (2.09–7.26) | <0.001 |
| underlying respiratory disease | 2.0 (1.08–3.82) | 0.028 |
| *C. auris* and *C. krusei* (model = AUC: 86.5%, accuracy: 77.3%, $R^2 = 0.558$, $P < 0.001$) | | |
| northern India ICU | 12 (4.8–34.1) | <0.001 |
| urinary catheter | 13 (4.93–35.5) | <0.001 |
| broad-spectrum antibiotics | 0.06 (0.009–0.475) | 0.007 |
| *C. auris* and *C. glabrata* (model = AUC: 62.2%, accuracy: 62.2%, $R^2 = 0.081$, $P < 0.011$) | | |
| northern India ICU | 2.8 (1.4–5.6) | 0.003 |

Only those variables with *P* values ≤0.05 are included. The following variables were also assessed: gender, respiratory distress, postoperative, trauma, burn, total parenteral nutrition (TPN), central venous catheterization, drainage catheter, abdominal catheter, intraperitoneal catheter, thoracic catheter, urinary catheter, underlying respiratory disease, underlying cardiovascular disease, underlying renal disease, previous antifungal, broad-spectrum antibiotics, immunodeficiency, malignancy, transplantation, low-birthweight neonates, premature neonates, neutropenia.

antifungal exposure exerted selective pressure for *C. auris*. Prior antifungal exposure was noted in 33%–58% of patients in earlier studies.[3,5,6] The present study predicts a model to identify susceptible populations. Patients with sepsis, undergoing invasive management for longer periods and exposed to antifungal agents should be investigated for *C. auris* candidaemia in India. Although the presence of respiratory illness was a significant risk factor in our model, there were no significant associations noted with mechanical ventilation or tracheostomy or antibiotic use.

The identification of *C. auris* in a routine laboratory may be difficult, as some automated identification systems misidentify this agent as *Candida haemulonii/Candida famata/Candida sake* or *Rhodotorula glutinis*.[3,5,6,8,21] Our *C. auris* isolates could grow at 42 °C, but failed to grow in the presence of 0.01% or 0.1% cycloheximide. These characteristics could help to presumptively differentiate *C. auris* from *C. haemulonii* in the majority of Indian laboratories, as they rely on conventional phenotypic identification and are not equipped with DNA sequencers or matrix MALDI-TOF biotypers. In our earlier study, *C. auris* isolates could be identified by MALDI-TOF after improving the database.[22] Similar observations were made by other studies.[21,23,24] MALDI-TOF can be used in routine laboratories for rapid identification of *C. auris* isolates.

The clonality of Indian isolates and the difference from Korean and Japanese isolates was reported earlier.[3] The AFLP fingerprinting in the present study confirmed the clonality of Indian *C. auris* isolates. Clustering of cases by country was reported, indicating geographical strain variability.[3,9,13,23,24] Although the AFLP method may not be as discriminatory as whole genome sequencing, it is one of the more highly discriminatory typing techniques, and can compare genomic characteristics of isolates quickly.

The 30 day crude and attributable mortality of 41.9% and 27% respectively in *C. auris* candidaemia were higher compared with non-*auris* candidaemia. The findings are similar to earlier studies on *C. auris* candidaemia with overall mortality ranging from 28.0% to 50.0%.[2,3,20] Owing to its decreased susceptibility to azoles, it is difficult to treat *C. auris* candidaemia cases.[2–4,6,8,25,26] *C. auris* isolates had high MICs even of isavuconazole and posaconazole.[3] A large number of isolates (58.1%) in the present study showed resistance to fluconazole. The patients with *C. auris* infection also

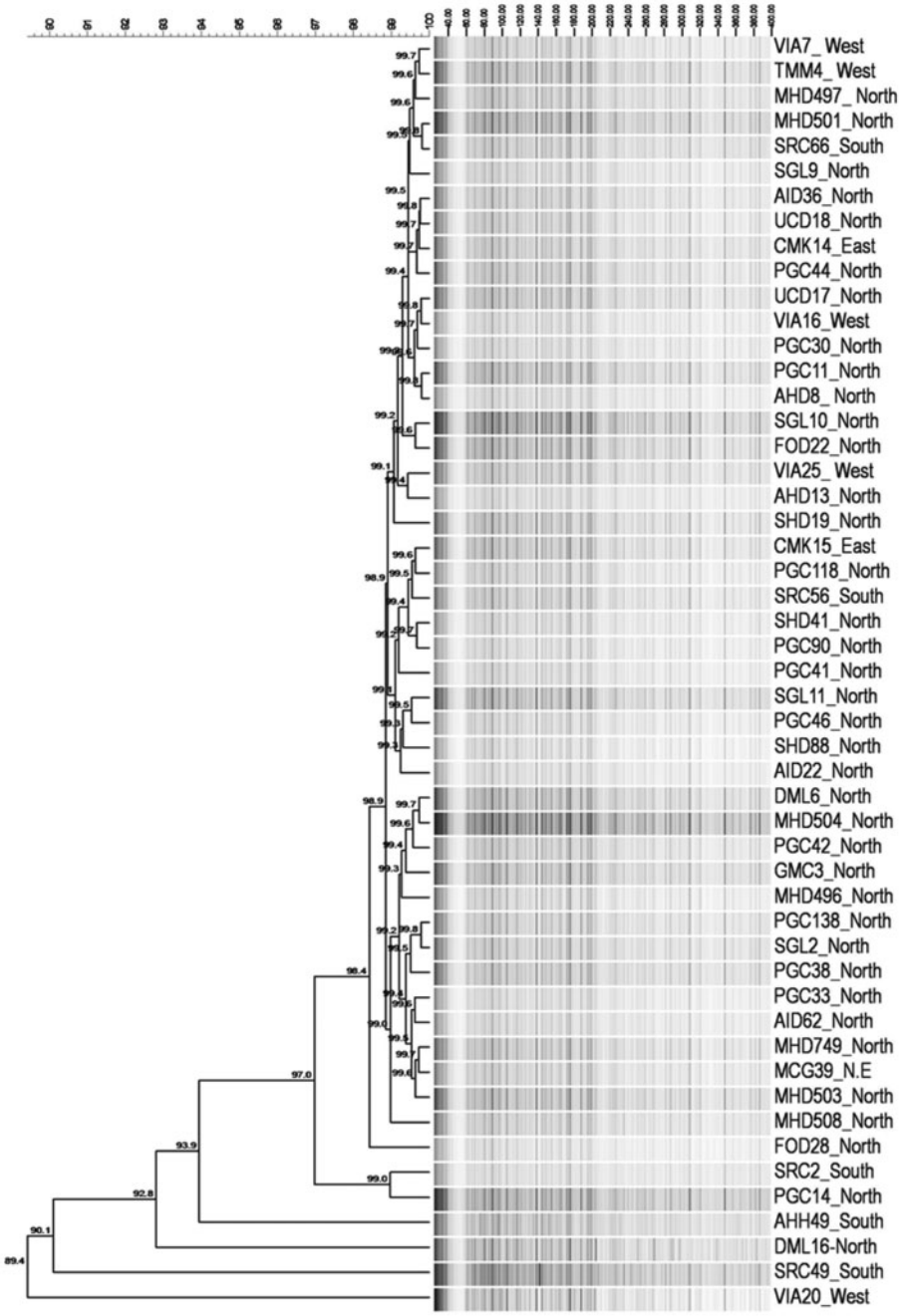


**Figure 1.** Phylogenetic tree constructed by UPGMA (unweighted pair group method with arithmetic mean) with 1000 bootstrap replications in combination with Pearson's correlation coefficient.

had higher fluconazole exposure prior to candidaemia diagnosis. The emergence of a few isolates with high MICs of caspofungin (9.5%) is a major concern, as an echinocandin is the first line of choice to treat candidaemia in the ICU.[27] However, due to the high variability of *in vitro* susceptibility testing results for caspofungin by the CLSI method, these results need to be interpreted with caution.[28] Of our isolates, 13% had an MIC >1 mg/L against amphotericin B. A similar observation was noted in Korean isolates;[5] whereas 50% of the isolates from Venezuela showed high amphotericin B MIC (>1 mg/L).[20] All these studies indicate that the *in vitro* susceptibility of *C. auris* to amphotericin B varies widely. The present study also demonstrated cross-resistance to the triazole group of antifungal agents in 14.8% of the isolates and multidrug resistance in 16.2% of isolates. The present study has certain limitations, as the study was not primarily aimed at evaluating the epidemiology of *C. auris* candidaemia. It is a subgroup analysis of a previously conducted study. The study did not look into colonization or the possible source of the agent in the

**Table 3.** *In vitro* antifungal susceptibility parameters of *C. auris* as determined by CLSI broth microdilution

| | No. of isolates inhibited at indicated MIC (mg/L), $n = 74$ | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1.0 | 2.0 | 4.0 | 8.0 | 16.0 | 32.0 | 64.0 | >64 | GM | $MIC_{50}$ | $MIC_{90}$ |
| AMB | 0 | 5 | 13 | 6 | 10 | 30 | 9 | 0 | 1 | 0 | 0 | 0 | 0 | 0.52 | 1.0 | 2 |
| FLC | 0 | 0 | 3 | 1 | 2 | 2 | 1 | 1 | 7 | 8 | 6 | 13 | 30 | 29.36 | 64.0 | >64 |
| VRC | 13 | 1 | 5 | 9 | 17 | 20 | 7 | 2 | 0 | 0 | 0 | 0 | 0 | 0.36 | 0.50 | 2 |
| ITC | 33 | 7 | 11 | 16 | 4 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0.08 | 0.06 | 0.25 |
| POS | 22 | 12 | 22 | 13 | 2 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0.10 | 0.12 | 0.25 |
| CAS | 0 | 0 | 4 | 10 | 16 | 26 | 11 | 7 | 0 | 0 | 0 | 0 | 0 | 0.80 | 1.0 | 2 |
| ANF | 15 | 13 | 15 | 9 | 7 | 12 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0.16 | 0.12 | 0.5 |
| MCF | 21 | 10 | 14 | 15 | 7 | 5 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0.12 | 0.12 | 1 |

AMB, amphotericin B; FLC, fluconazole; VRC, voriconazole; ITC, itraconazole; POS, posaconazole; CAS, caspofungin; ANF, anidulafungin; MCF, micafungin; GM, geometric mean; $MIC_{50}$, concentration at which 50% of the isolates are inhibited; $MIC_{90}$, concentration at which 90% of the isolates are inhibited. Some of these data have been published previously.[9]

environment and the transmission mechanism. A systematic epidemiological investigation would help to describe the natural history of the disease.

In conclusion, the present study confirms the spread of MDR *C. auris* candidaemia in ICUs across India. Invasive intervention in ICUs may lead to nosocomial acquisition of *C. auris* infection. As the majority of the isolates are of clonal origin and invasive procedures are risk factors, it is important to study the source of the agent and the transmission mechanism. Until such detailed epidemiological studies are conducted, the providers of critical care in Indian ICUs should be vigilant for *C. auris* infection in patients with sepsis, especially those with longer ICU stay and antifungal exposure, as these are two important risk factors identified.

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## Transparency declarations

None of the authors has any conflict of interest. The funding agency did not participate or interfere in any stage of the study. All authors had full access to all trial data and take responsibility for the integrity of the data and the accuracy of the data analysis.

### *Author contributions*

Study concept and design: A. C. and S. M. R.; acquisition, analysis, or interpretation of data: S. M. R., R. A. P., P. Sood and H. K.; Drafting of the manuscript: S. M. R., A. C., H. K. and R. A. P; critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: R. A. P., P. Singh and P. Sood; administrative, technical or material support: A. C., S. M. R., M. R. C., R. A. P., A. J. K., R. S. K. M., A. A., R. S., S. D., D. C., A. P., I. X., B. T. and A. G.; study supervision: A. C. and S. M. R.

## Supplementary data

Supplementary Methods and Tables S1–S6 are available at *JAC* Online (http://jac.oxfordjournals.org/).

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