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Review

Candida auris—a systematic review to inform the world health organization fungal priority pathogens list

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Abstract

The World Health Organization (WHO) in 2022 developed a fungal priority pathogen list. *Candida auris* was ultimately ranked as a critical priority pathogen. PubMed and Web of Science were used to find studies published from 1 January 2011 to 18 February 2021, reporting on predefined criteria including: mortality, morbidity (i.e., hospitalization and disability), drug resistance, preventability, yearly incidence, and distribution/emergence. Thirty-seven studies were included in the final analysis. The overall and 30-day mortality rates associated with *C. auris* candidaemia ranged from 29% to 62% and 23% to 67%, respectively. The median length of hospital stay was 46–68 days, ranging up to 140 days. Late-onset complications of *C. auris* candidaemia included metastatic septic complications. Resistance rates to fluconazole were as high as 87%–100%. Susceptibility to isavuconazole, itraconazole, and posaconazole varied with MIC90 values of 0.06–1.0 mg/l. Resistance rates to voriconazole ranged widely from 28% to 98%. Resistance rates ranged between 8% and 35% for amphotericin B and 0%–8% for echinocandins. Over the last ten years, outbreaks due to *C. auris* have been reported in in all WHO regions. Given the outbreak potential of *C. auris*, the emergence and spread of MDR strains, and the challenges associated with its identification, and eradication of its environmental sources in healthcare settings, prevention and control measures based on the identified risk factors should be evaluated for their effectiveness and feasibility. Global surveillance studies could better inform the incidence rates and distribution patterns to evaluate the global burden of *C. auris* infections.

Key words: *Candida auris*, mortality, drug resistance, prevention, epidemiology.

Introduction

Fungal pathogens pose a global threat to human health and are associated with high mortality. Although efforts have been made to estimate the burden, there is insufficient formal surveillance data available to allow accurate measurements to be made.[1] Human fungal pathogens tend to affect immunocompromised individuals (e.g., those diagnosed with cancer, chronic lung disease, or tuberculosis), and may cause invasive fungal disease (IFD), among other conditions.[1,2] IFD can be life-threatening for hospitalized patients and frequently result in high healthcare costs.[1,3]

In response to the growing global challenge of fungal pathogens, in 2022 the World Health Organization (WHO) published its first fungal priority pathogens list (FPPL).[4] The FPPL was developed through a comprehensive international consultation process, utilizing a Multiple Criteria Decision Analyses (MCDA) approach, including a global Discrete Choice Experiment (DCE) survey to establish weights for

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10 predefined prioritization criteria. Each fungal pathogen was subsequently ranked according to data from systematic reviews and based on the outcomes of the DCE. *Candida auris* was pre-selected for prioritization in the FPPL due to its rapid emergence worldwide, multidrug resistance, and high mortality rates of 30%–60%.[5] From its discovery in 2009 to 2023, *C. auris* has been isolated in over 50 countries across six continents.[6,7] Its rapid transmissibility has resulted in many outbreaks worldwide.[6] *Candida auris* arose simultaneously and independently across four regions of the world, as confirmed by whole genome sequencing.[8] Isolates were classified geographically into six main clades differing from each other by thousands of single-nucleotide polymorphisms: clade I (Southern Asia), clade II (Eastern Asia), clade III (Africa), clade IV (South America), clade V (Iran), and clade VI (Indo-Malaysian).[8–10] There is phylogeographic mixing of the clades, except for clade IV, with a more defined phylogeographic substructure.[11] Clades V and VI reveal the unknown genetic diversity and origin of *C. auris*, highlighting the importance of active surveillance in clinical settings to track its transmission. Unlike other *Candida* species, *C. auris* is difficult to identify using conventional phenotypic methods such as VITEK 2 in routine clinical laboratories.[12] *Candida auris* on VITEK 2 can be misidentified as *C. haemulonii, C. duobushaemulonii, C. lusitaniae*, and *C. famata* despite being able to differentiate some clades.[12] There are several FDA-approved molecular tests such as (i) Bruker Biotyper brand MALDI-TOF using the updated Bruker FDA-approved MALDI Biotyper CA System library (Version Claim 4), (ii) bioMérieux VITEK (MALDI-TOF) MS using the FDA-approved IVD v3.2, (iii) GenMark ePlex Blood Culture Identification Fungal Pathogen (BCID-FP) Panel, and (iv) BioFire FilmArray BCID2.[12] Although molecular tests are widely used worldwide, they are still limited or absent in low- and middle-income countries (LMICs).[13] As a result, the incidence of *C. auris* infections is likely to be underestimated, and its management could be suboptimal. In addition, *C. auris* infection transmission prevention, control, and eradication are extremely challenging, outbreak containment is associated with high cost to healthcare facilities. It is important to emphasize that the high mortality associated with *C. auris* infections underscores the urgent need for effective prevention, early detection, and treatment strategies to combat this emerging pathogen.

Despite the global concern, limited research has been performed to support the effective diagnosis and treatment strategies for *C. auris* infections.[14] This systematic review was undertaken to inform the WHO FPPL process, with specific aims to (1) evaluate the features and global impact of invasive infections caused by *C. auris* and (2) determine knowledge gaps for *C. auris* to highlight research needs.

Methods

Study design

We performed a systematic review following the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.

Inclusion and exclusion criteria

The criteria for the prioritization used to evaluate features and global impacts of IFD caused by *C. auris* included mortality, hospitalization, disability, antifungal drug resistance, preventability, annual incidence, the global distribution, and emergence in the last decade. Studies were included if they satisfied the following criteria: (1) patient population included adults and/or paediatrics; (2) included data on *C. auris*; (3) included data on ≥ 1 outcome criterion; (4) were either retrospective or prospective observational studies, randomized controlled trials, reports on epidemiology or surveillance; and (5) articles had to be published from 1 Jan 2011 to 18 Feb 2021. Studies reporting on the following criteria were excluded: (1) non-human data, (2) non-fungal data, (3) no data on the selected outcome criteria, (4) inferences based on < 50 patients or isolates, (5) new antifungal agents (in pre-clinical, early phase trials or not licensed), (6) new diagnostic tools (not registered for routine clinical use), (7) *in vitro* studies of resistance mechanism(s), (8) case reports, conferences, abstracts, or reviews, (9) articles written in languages other than English, and (10) articles published outside the study period.

Search strategy

A search on the PubMed and Web of Science databases was performed for potentially eligible studies published between 1 Jan 2011 and 18 Feb 2021. On PubMed, the search was optimized using the medical subject headings (MeSH) and/or keyword terms in the title/abstract for *C. auris* and criterion. The final search used was (*C. auris* [Title/Abstract]) combined, using AND terms, with criteria terms including (mortality [MeSH Terms]) OR (morbidity [MeSH Terms]) OR (hospitalization [MeSH Terms]) OR (disability [All Fields]) OR (drug resistance, fungal [MeSH Terms]) OR (prevention and control [MeSH Subheading]) OR (disease transmission, infectious [MeSH Terms]) OR (diagnostic [Title/Abstract]) OR (antifungal agents [MeSH Terms]) OR (epidemiology [MeSH Terms]) OR (surveillance [Title/Abstract]).

On Web of Science, MeSH terms are not available and therefore a topic search (TS), title (TI), or abstract (AB) search was used. The final search used [TI=('*Candida auris*') OR AB=('*Candida auris* ')], combined using AND terms, with criteria terms each as topic search, including (mortality) OR (case fatality) OR (morbidity) OR (hospitalization) OR (disability) OR (drug resistance) OR (prevention and control) OR (disease transmission) OR (diagnostic) OR (antifungal agents) OR (epidemiology) OR (surveillance).

Study selection

Articles searched from each database were incorporated into a reference manager, EndNote®. These search results were assessed using the online systematic review software, Covidence® (Veritas Health Innovation, Australia). After removing duplicate articles, the title and abstract of the remaining were screened as per the inclusion criteria. The reasons for excluding articles were recorded during full-text screening. The title/abstract and full-text screenings were undertaken independently by two reviewers (HYK and TAN). A third reviewer (JWA) resolved disagreements. Relevant articles identified from the reference list of the included articles were added.

Data extraction and synthesis

One reviewer extracted data from the included studies for each relevant criterion and a second reviewer reviewed them independently. We synthesized the extracted data on the outcome criteria either quantitatively or qualitatively, based on the quality and nature of the data. An independent assessment

of retrieved literature and analysis was conducted by senior mycology experts from the WHO FPPL advisory group.

Risk of bias assessment

Two reviewers independently assessed the risk of bias for the included studies on relevant bias criteria. The risk of bias tool for randomized trials version 2 (ROB 2) tool [15] was used to assess the randomized controlled trials, and the risk of bias in non-randomized studies (RoBANS) tool [16] was used for non-randomized trials. The studies were categorized as low, high, and unclear risk. Each outcome criterion was assessed to determine whether any bias possibly occurred based on the study design, data collection, or analysis in that study for the selected outcomes.

Results

Study selection

A total of 699 articles were identified in PubMed ($n = 333$) and the Web of Science Core Collection ($n = 366$) databases. Duplicate and non-relevant articles were excluded. The remaining of 46 articles underwent full-text screening of which 37 articles were included in the final analysis (Fig. 1). No additional articles were identified by the senior experts from the WHO FPPL AG.

Risk of bias

Thirty-three of the included studies were rated as low risk of bias in all the domains evaluated (Table 1). Three studies were rated as unclear risk of bias, potentially because of selection biases due to unclear eligibility criteria or population groups. One study[17] was considered as having a high risk of bias due to selecting only a proportion of isolates for drug susceptibility, without justification for the selection.

Death

The overall mortality rates in patients with *C. auris* infection[8,18, 21, 22, 25, 46, 47, 51] or candidaemia[18,21,25, 46, 47, 51] ranged from 29% to 62% (Table 2). The lowest overall mortality rate was 29% in a study of 77 patients with candidaemia from Kenya,[18] while the highest mortality rate was reported in a study from Pakistan (62.2%) based on data from 37 patients with candidaemia.[47] Eight studies reported the 30-day crude mortality in *C. auris*-infected patients ranging from 23.4% to 66.7%,[19, 23, 24, 41–43, 49] and in two studies, the mortality of 27%–31% could be attributed to *C. auris*.[41,49] A low rate (14%) of 30-day mortality was based on only 14 patients with *C. auris* infection in England, rising to 29% by 90-days.[50] Of all 19 studies, three studies[17,29,48] might have a risk of bias for analysis of mortality because they did not differentiate patients with *C. auris* colonization from those with infection. One study from an ongoing outbreak reported a mortality of 0% at the time of the publication.[48] Differences in overall or 30-day crude mortality were not observed between *C. auris* vs. *C. albicans*[18,41] or between *C. auris* vs. non-*C. auris* species.[18,47,51,41,49] These variations in mortality rates can be attributed to differences in study populations, geographic locations, healthcare infrastructure, and the emergence of multidrug-resistant strains.

Inpatient care

Patients with *C. auris* candidaemia had longer lengths of hospital or intensive care unit (ICU) stay than those with other candidaemias (Table 3).[25,47] Lengths of ICU stay of > 2 weeks were reported for 70% of *C. auris* candidaemia patients.[24] Similarly, other studies reported > 2 weeks of hospital stay in 78% of *C. auris* candidaemia patients,[47] and even longer (> 55 days) in 47% of *C. auris* candidaemia patients.[21] The median lengths of stay of 49 and 68 days for public and private hospitals in South Africa were reported, respectively.[51] A comparable median stay of 46 days was reported in a study involving both adult and paediatric *C. auris* candidaemia patients (median age of 23 years old).[23] Another study from Pakistan reported a slightly lower median length of stay of 25 days, in a mixed group of both *C. auris* candidaemia or non-candidaemia.[46]

Antifungal resistance

In total, 25 studies reported on the drug susceptibility and/or resistance rates of *C. auris* (Table 4). Susceptibility data to azoles and other antifungal drugs are presented in Tables 5 and 6, respectively. Studies used a range of testing methodologies but the same 'tentative breakpoints' due to the lack of *C. auris*-specific breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) and European Committee for Antimicrobial Susceptibility Testing (EUCAST). Tentative breakpoints were set by the US Centers for Disease Control and Prevention (CDC) based on breakpoints established for *Candida* species closely related to *C. auris*.[53,54] In circumstances where no CDC clinical MIC breakpoints are established, tentative interpretative criteria were defined based on breakpoints established for other *Candida* species or upper limit of the wild-type distribution (epidemiological cutoff values—ECVs or ECOFFs) from the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Regarding antifungal susceptibility, in most studies, resistance rates to fluconazole were observed to be as high as 87%–100%.[8, 19, 20, 21, 26, 29, 32, 37, 46, 52] On the other hand, susceptibility to other azoles was variable between the studies. Isavuconazole MIC90 values ranged from 0.38 to 1.0 based on E-test or CLSI broth microdilution.[27, 37, 52] A lower range of isavuconazole MIC90 values, between 0.12 and 0.25 was also reported using EUCAST broth microdilution and MIC Test Strip (MTS) methods, respectively.[44] Itraconazole MIC90 values ranged from 0.12 to 1,[8, 27, 37, 41, 44, 52] with one study reporting moderate to high non-wild-type rates of 88% in candidaemia isolates and 39% in colonization isolates.[21] Posaconazole MIC90 values similarly ranged from 0.06 to 1[8, 27, 37, 41, 44, 52] and a low non-wild-type rate of 6% was reported in candidaemia patients.[21] An exception was a single-centre study in an ICU setting in the UK reporting a 90% non-wild-type rate to posaconazole.[29] Non-wild-type rates to voriconazole varied from 28% to 98%.[8, 20, 21, 29, 32, 46, 52]

Relatively moderate resistance rates to amphotericin B were observed ranging from 8% to 35%,[8, 19, 20, 26, 28, 29, 32, 46] although some studies reported no resistance (0%),[21, 35, 37] and one reported a high resistance rate of 58%–61% during an outbreak in New York.[52] A low resistance rate to echinocandins was observed, between 0% and 8%.[8, 19, 21, 26, 28, 29, 32, 35, 37, 46, 52]

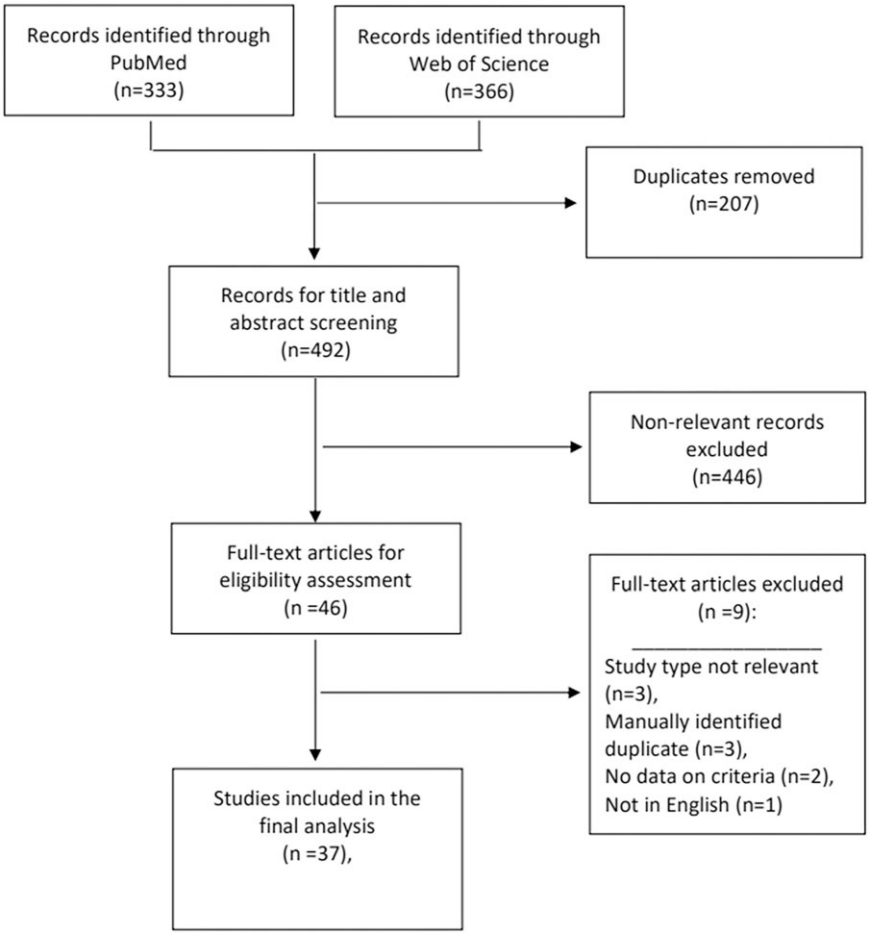

Figure 1. PRISMA flow diagram for selection of studies included in the systematic review.

Limited data were available to assess the susceptibility of *C. auris* to nystatin and terbinafine, although one study reported MIC90s of 4 and 32, respectively.[27]

Preventability of infection

Significant ($P < 0.05$) risk factors for developing *C. auris* infection or candidaemia (Table 7) included renal impairment (OR 1.35–2.31) [18,30] and cardiothoracic unit or intensive care unit (ICU) stay of > 10–15 days (OR 2.76–5.11).[18,25,29] Other risk factors were related to ICU settings, including the use of mechanical ventilation (OR 2.43–3.17),[18,42] central venous catheter (CVC) (as high as OR 4.61–13.48),[18,42] total parenteral nutrition (OR 3.49–3.73)[30,42] and sepsis (OR 1.75–3.47) (all $P < 0.05$).[25,30] Previous use of antifungal drugs (especially triazoles, followed by echinocandins) in the last 30 days of candidaemia diagnosis, was also a risk factor for *C. auris* (OR 1.17–2.8,[30,41,51] as high as OR 38.3,[47] $P < 0.05$ in 3/4 studies).

Candida auris has emerged as a cause of hospital outbreaks associated with patient carriage or environmental surface contamination,[17,19,21,22,23,24,25,26,29,38,42,43,44,48,50,52] which highlights that adequate laboratory capacity and infection control preparedness are required to prevent spread within hospitals. Illustrative is the *C. auris* colonization in ventilator-capable skilled nursing facility settings in the period 2016–2018.[38]

Annual incidence of infections

The annual incidence rates of *C. auris* infection could not be assessed from the included studies.

Global distribution

In the last ten years, outbreaks and invasive healthcare-associated infections due to *C. auris* have been reported in all six WHO regions, as evidenced in many included studies (Table 8).[8,17–44,46–52] Five studies provided data on distribution of *C. auris* in different countries. Prevalence of *C. auris* in hospitalized candidaemia patients in Kenya ranged from 11% to 54% between 2011–2016, with lowest rates (11%–28%) observed during 2015 and 2016.[18] During the comparable period, in 2016–2017, the reported *C. auris* prevalence among candidaemia cases in South Africa from 269 hospitals was 14%.[51] *Candida auris* prevalence in India varied between studies. A multi-centre study in India reported a low rate of 5.3% *C. auris* cases in candidaemia patients from 27 ICUs between 2011 and 2012.[41] In comparison, a higher prevalence rate of 39% was reported in India during 2016–2017, although based on a single centre.[49]

Trends in the last 10 years

Candida auris was first reported in 2009 after isolation from ear cultures, followed by isolation from blood cultures in 2011.[35] During the last 10 years, outbreaks or in-

Table 1. Risk of bias of included studies.

Author	Year	Final risk (low, high, and unclear)
Adam[18]	2019	Low
Adams[19]	2018	Low
Ahmad[20]	2020	Unclear
Al Maani[17]	2019	High
Alfouzan[21]	2020	Low
Al-Rashdi[22]	2021	Low
Armstrong[23]	2019	Low
Bayona[24]	2020	Low
Caceres[25]	2020	Low
Chow[26]	2018	Low
Chowdhary[27]	2018	Low
Escandón[28]	2018	Low
Eyre[29]	2018	Low
Garcia- Bustos[30]	2020	Low
Govender[31]	2018	Low
Khan[32]	2018	Low
Kohlenberg [33]	2018	Low
Kordalewska[34]	2018	Unclear
Kwon[35]	2019	Low
Law[36]	2020	Low
Lockhart[8]	2017	Low
Magobo[37]	2020	Low
Pacilli[38]	2020	Low
Pfaller[39]	2019	Low
Plachouras[40]	2020	Low
Rudramurthy[41]	2017	Low
Ruiz-Gaitan[42]	2019	Low
Ruiz-Gaitan[43]	2018	Low
Ruiz-Gaitan[44]	2019	Unclear
Savage-Reid[45]	2020	Low
Sayeed[46]	2019	Low
Sayeed[47]	2020	Low
Schelenz[48]	2016	Low
Shastri[49]	2020	Low
Taori[50]	2019	Low
van Schalkwyk[51]	2019	Low
Zhu[52]	2020	Low

vasive healthcare-associated infections due to *C. auris* have been reported in many countries across all six WHO regions[8, 17–44, 46–52] Trends in *C. auris* emergence were assessed based on two studies. A single-centre study in Kenya reported increasing *C. auris* in patients with candidaemia from 35% in 2011 to 54% by 2014, although a lower rate of 11%–28% was reported in 2015–2016.[18] No data were available to assess the trend after these years.

A point prevalence survey conducted at one ventilator-capable skilled nursing facility in the USA during 2018 reported an increasing *C. auris* prevalence from 43% to 71%.[38]

Discussion

Mortality in patients with *C. auris* infection or candidaemia is substantial. It may be partially explained by factors including delays in species-level identification in routine practice, presence of severe underlying co-morbidities, and antifungal resistance.[55,56] It has been suggested that variability in mortality may be related the variation of *C. auris*'s virulence, i.e., cytotoxic and inflammatory effects on host skin, within species (different clades).[57] Geographic variability in mortality rates could also be explained by differences in underlying diseases in populations affected or the capacity of healthcare systems, including diagnostic and therapeutic capacities. The included studies reported challenges with identifying deaths attributable to *C. auris* infection, although two studies reported attributable case-fatality rates of 27%–31% to *C. auris* infection.[41,49] In the study of 27 Indian ICUs, the 30-day attributable case fatality rate for *C. auris* infection (ascertained by clinical judgement and microbiology tests) was comparable to or higher than those for non-*C. auris* infections (27% *C. auris* vs. 25.6% *C. albicans*, 24.5% *C. tropicalis*, 18.4% *C. parapsilosis*, 10.5% *Pichia kudriavzevii* [formerly *C. krusei*], and 24.3% *Nakaseomyces glabrata* [formerly *C. glabrata*]). In contrast, animal studies compared between-species virulence and demonstrated that the virulence of *C. auris* (e.g., survival time, survival percentages, fungal load, and tissue damage in tested organs) was less than or comparable to *C. albicans*[58–60] and higher than *C. parapsilosis, P. kudriavzevii*, and *N. glabrata*.[58,61–64] On balance, the high case-fatality rates observed may be more related to host factors than increased virulence of the organism, although further studies are needed.

Predictors of *C. auris*-associated mortality included haemodialysis (OR 8.3), central venous catheter (CVC) (OR 4.6), congestive heart failure (OR 4.23), candidaemia (OR 3.5), total parenteral nutrition (OR 3.3), renal impairment (OR 3.0), bacterial co-infection (OR 2.1), and invasive ventilator (OR 1.7) (all $P < 0.05$), informed by a multi-centre study across five countries.[65]

A prognostic analysis from a single-centre study in Pakistan found that candidaemia (adjusted OR 4.2, $P = 0.037$) was again associated with higher mortality, while source control, defined as the removal of inciting agent or focus and entailed the removal of central line in case of Central Line Associated Blood Stream Infection (CLABSI), Foley's catheter in Catheter Associated Urinary Tract Infection (CAUTI), exploratory laparotomy in peritonitis, drainage of pus collection, and removal of lumbar drain in ventriculitis, (OR 0.2, $P = 0.038$) was associated with lower mortality.[46] Kidney disease (mostly chronic kidney disease and nephrotic syndrome) was found to be a predictor of mortality in a univariable analysis of 912 patients ($P = 0.029$).[66] Possible explanations for this may include (1) weaken immunity due to low protein and malnutrition associated with kidney disease,[67] the use of immunosuppressants to treat kidney disease,[68] and (2) haemodialysis treatment for certain patients with kidney disease.[69] Overall, *C. auris*-associated mortality is likely multifactorial and is related to comorbidities, poor infection prevention control measures, complications of invasive procedures, plus diagnostic and treatment delays.

Overall, patients with *C. auris* candidaemia had longer lengths of hospital or ICU stay than those with other candidaemias. This might be explained by virulence factors, such as the ability of *C. auris* to form aggregates that hinder the host immune system, persist in host tissues, and tolerate antifungals.[58] Additionally, inadequate therapy may result in treatment failure, related to late species identification or misclassification with its close relatives [56] and/or acquired resistance to commonly used empiric antifungals.[70] Late-onset complications in patients with *C. auris* candidaemia have been reported in < 10% of the cases and included septic metastatic complications (spondylodiscitis, endocarditis, and ventriculitis).[43]

Risk factors for developing *C. auris* infection included long ICU stay (> 10–15 days) and other ICU-related factors (mechanical ventilation, CVC, total parenteral nutrition, and sepsis). *Candida auris* has a propensity to persist on healthcare

Table 2. Mortality associated with *C. auris*.

Author	Study design		Study period	Country	Level of care	Population description	Number of patients	Mortality type, %
Adam[18]	Retrospective cohort study	Single centre	09/2010-12/2016	Kenya	Tertiary	Hospitalized patients with at least one *Candida*-positive blood culture	77	Overall mortality: candidaemia 22/77, 29% (*C. albicans*, 26%; Other *Candida* species 39%)
Adams[19]	Case series	Multi-centre	05/2013-04/2017	USA	Tertiary	Patients with culture positive *C. auris*	51	30-day mortality: candidaemia 12/31, 39% 90-day mortality: 18/31, 58% The number of deaths attributable to *C. auris* infection is unknown.
Al Maani[17]	Case series	Single centre	04/2018-04/2019	Oman	Secondary	Patients admitted for > 48 hours with a positive *C. auris*	25	Overall mortality: 17/31, 53.1%
Alfouzan[21]	Case series	Single centre	01/2018-06/2019	Kuwait	Secondary	Patients who yielded *C. auris* from bloodstream or other site	17	Candidaemia 10/17, 58.8% Colonized 27/54, 50%
Al-Rashdi[22]	Case series	Multi-centre	01/2019-12/2019	Oman	Tertiary	Symptomatic and screened hospital in patients with positive *C. auris* isolate	108	Overall: colonization or infection 42/108, 38.9% Infection 32/61, 52.5%
Lockhart[8]	Case series	Multi-centre	2008 2012-2015	Pakistan ($N = 18$) India ($N = 19$) South Africa ($N = 10$) Venezuela ($N = 5$) Japan ($N = 1$)	Tertiary	Hospital patients with positive *C. auris* isolate	41	In-hospital deaths: infection 24/41, 59%
Armstrong[23]	Case series	Multi-centre	01/2015-09/2016	Colombia	Tertiary	Hospital inpatients (including paediatrics) with *C. auris* candidaemia	40	30-day mortality: candidaemia 17/40, 43%
Bayona[24]	Case series	Single centre	10/2017-06/2020	Spain	Tertiary	ICU patients with positive *C. auris* screening colonization study or *C. auris* candidaemia	47	30-day mortality: candidaemia 11/47, 23.4%
Caceres[25]	Case control study	Multi-centre	01/2015-09/2016	Colombia	Tertiary	Patients with *C. auris* candidaemia or non-*C. auris* candidaemia (excluding *C. haemulonii*, *C. sake*, and *Candida* spp. due to potential for misidentification as *C. auris*)	40	Overall mortality in candidaemia 23/40, 57% 30-day mortality in candidaemia: 17/40, 43%

Table 2. Continued

Author	Study design		Study period	Country	Level of care	Population description	Number of patients	Mortality type, %
Eyre[29]	Case control study	Multi-centre	02/2015-08/2017	England	Tertiary	Neurosciences ICU patients	66	30-day mortality: colonization or infection 11/66, 17% 90-day mortality: colonization or infection 13/64, 20%
Rudramurthy[41]	Prospective cohort study	Multi-centre	04/2011-09/2012	India	Tertiary	ICU patients who acquired candidaemia in ICU	74	Crude 30-day mortality: candidaemia 31/74, 41.9% (*C. albicans*, 37.5%; *C. tropicalis* 35.4%, *C. parapsilosis* 31.9%) Attributable 30-day mortality: candidaemia 20/74, 27%
Ruiz-Gaitan[42]	Case control study	Single centre	04/2016-02/2017	Spain	Tertiary	Patients admitted to surgical ICU or medical ICU	41	30-day mortality in candidaemia: 42/79, 58.2%
Ruiz-Gaitan[43]	Case series	Single centre	04/2016-01/2017	Spain	Tertiary	*Candida auris* positive patients (colonized and infection)	41	30-day mortality in candidaemia: 17/41, 41.4% (attributable mortality rate for *C. auris* candidaemia was difficult to assess)
Sayeed[46]	Retrospective cohort study	Single centre	09/2014-04/2017	Pakistan	Tertiary	Hospitalized patients with positive *C. auris* culture	65	Overall: colonization or infection 39/92, 42% 14-day mortality: colonization or infection 29/92, 32% *C. auris* attributable: colonization or infection 11/92, 12% Mortality in infection 30/65, 46.2%, Mortality in candidaemia: 23/38, 60.5%
Sayeed[47]	Retrospective cohort study	Single centre	09/2014-03/2017	Pakistan	Tertiary	Patients aged > 16 with candidaemia	37	Overall: candidaemia 23/37, 62.2% (non-*C. auris* 52.5%) 14-day mortality: 17/37, 45.9%

Table 2. Continued

Author	Study design		Study period	Country	Level of care	Population description	Number of patients	Mortality type, %
Schelenz[48]	Case series	Single centre	04/2015-07/2016	England	Tertiary	Hospitalized patients with positive *C. auris* isolate	22	Overall: colonization or infection 0/50, 0%
Shastri[49]	Prospective cohort study	Single centre	04/2016-09/2017	India	Tertiary	Patients developing candidaemia 48 hours after ICU admission	42	Crude 30-day mortality: candidaemia 28/42, 66.7% (all candidaemia 61.0%) 30-day mortality attributable to *C. auris*: candidaemia 13/42, 30.9% (all candidaemia 26.8%)
Taori[50]	Retrospective cohort study	Single centre	04/2016-02/2017	England	Tertiary	Hospitalized patients with positive *C. auris* isolates	14	30-day mortality: Infection 2/14, 14.3% 90-day mortality: 4/14, 28.6%
van Schalkwyk[51]	Retrospective cohort study	Multi-centre	01/2016-12/2017	South Africa	Tertiary	Patients who had *Candida* species blood specimen processed by an NHLS or private-sector laboratory	794	Crude in-hospital case-facility rate (*C. auris*) candidaemia 46/102, 45.1% (non-*C. auris* 43%)

Abbreviations: ICU = intensive care unit, NHLS = National Health Laboratory Service.

environmental surfaces for up to 3 months,[71] which fosters its spread amongst hospital staff and patients. Patients in ICUs often undergo several invasive procedures; hence, exposure to reusable equipment contaminated by *C. auris* is likely. Once it enters a healthcare facility environment, C. *auris* eradication can be challenging. Therefore, adequate infection control preparedness is required to prevent hospital transmission within the hospitals, although optimal infection prevention strategies require further study. Several organizations such as the Australasian Society for Infectious Diseases (ASID), the US Center for Disease Control and Prevention (US CDC), or European Centre for Disease Control and Prevention (ECDC) have provided guidance for the prevention of *C. auris* outbreaks. Improving infection control, including (1) reinforcement of hand hygiene, (2) daily and terminal cleaning and disinfection of healthcare environment and shared equipment using an appropriate disinfectant, and (3) patient isolation, contact precaution, and screening of high-risk patients once *C. auris* is detected could help in reducing outbreaks.[72,73]

Previous use of antifungals, especially triazoles was associated with an increased risk for *C. auris* infection. Antifungals might disrupt micro- and mycobiome balance in mice gut as well as their healthy immune system.[74] Inappropriate use of broad-spectrum antifungals might also result in antifungal selection pressure.[75–77] A high proportion (59%–100%) of *C. auris* candidaemia patients had a history of antibiotic use, although the association was not statistically significant (hazard ratio [HR] 0.06; 95%CI 0.08–4.47).[30,66,78] *Candida auris* colonization is associated with a change in the skin microbiome, likely triggered by the use of antibiotics and harsh detergents.[79,80] Renal impairment is the another risk factor with multiple potential mechanisms, including (1) mononuclear cells seem to less respond to *Candida* antigen in uraemia[81] and (2) patients with renal impairment may require prolonged haemodialysis, which disrupts anatomical barriers via direct chronic mechanical contact with the vascular system, and impairs the host cellular defence.[82] Patients with multisite colonization (skin, respiratory, and/or urinary) have an increased risk of infection (adjusted hazard ratio [HR] 9.67, $P = 0.027$).[30,78] Based on risk factors identified, the effectiveness and feasibility of screening strategies and preventative measures (e.g., decolonization) need to be evaluated.

Resistance of *C. auris* to fluconazole was high (87%–100%) and its non-wild-type rates to other azoles were variable (0%–98%). *Candida auris* isolates showed relatively moderate resistance rates of 8%–35% to amphotericin B, and a lower resistance of 0%–8% to echinocandins. These percentages tend to differ according to the clades studied,[11] though the resistance/non-wild-type order of azoles > amphotericin B > echinocandins appeared consistent across the studies. Concerning the clade-wise susceptibility, eastern Asia clade had the highest percentage of susceptibility (86%), followed by Southern America clade (31%), Southern Asia clade (3%), and Africa clade (2%).[11] The high resistance rates to fluconazole might be associated with the fact that most isolates tested were from the highly fluconazole resistant Southern Asia and Southern Africa clades.[83] In fact, there were still a minority of susceptible isolates from the Eastern Asia[27,84] and Southern American clades.[28,85] The wide MICs distributions to other azoles suggest variable acquired resistance.[86] Owing to the unknown correlation between microbiologic breakpoints and clinical outcomes, a result of an elevated MIC for an antifungal should not necessarily exclude its use, espe-

Table 3. Length of hospital stay associated with *C. auris*.

Author	Year	Study design		Study period	Country	Level of care	Population description	Number of patients	Length of stay
Alfouzan[21]	2020	Case series	Single centre	01/2018-06/2019	Kuwait	Secondary	Patients who yielded *C. auris* from bloodstream or other site	17	<15 days in 1, 5.9% candidaemia 15–35 days in 5, 29.4% candidaemia 36–55 days in 3, 17.6% candidaemia > 55 days in 8, 47.1% candidaemia
Armstrong[23]	2019	Case series	Multi-centre	01/2015-09/2016	Colombia	Tertiary	Hospital inpatients (including paediatrics) with *C. auris* candidaemia	40	Median (IQR) 46 (34–69) days
Bayona[24]	2020	Case series	Single centre	10/2017-06/2020	Spain	Tertiary	ICU patients with *C. auris* colonization or *C. auris* candidaemia	47	ICU stay > 2 weeks—candidaemia patients only = 33/47, 70.2%
Sayeed[46]	2019	Retrospective cohort study	Single centre	09/2014-04/2017	Pakistan	Tertiary	Hospitalized patients with positive *C. auris* culture	65	Median (IQR) 25 (1–163) days
Sayeed[47]	2020	Retrospective cohort study	Single centre	09/2014-03/2017	Pakistan	Tertiary	Patients aged > 16 with candidaemia	37	In-Hospital stay > 15 days after admission = 29/37, 78.4% In-Hospital stay > 15 days after positive culture = 12/37, 32.4% Higher mean hospital stays (*C. auris* patients 36.32 days vs. non-*C. auris* patients 14.8 days, $P = < .001$) and higher > 15-day in-hospital stay from positive culture (HR 2.68, 95% CI: 1.1-6.3, $P = .025$).
Shastri[49]	2020	Prospective cohort study	Single centre	04/2016-09/2017	India	Tertiary	Patients developing candidaemia 48 hours after ICU admission	42	Hospital stay (*C. auris* candidaemia) (median, IQR) 18, 9–34.8 days
Taori[50]	2019	Retrospective cohort study	Single centre	04/2016-02/2017	England	Tertiary	Hospitalized patients with positive *C. auris*	14	Duration in hospital after colonization (> 30 days) (infection) 10/14, 71.4%
van Schalkwyk[51]	2019	Retrospective cohort study	Multi-centre	01/2016-12/2017	South Africa	Tertiary	Patients who had *Candida* species blood specimen processed by an NHLS or private-sector laboratory	794	Length of stay (*C. auris*, public sector hospitals, $n = 67$) median (IQR) = 49 (30–72) Length of stay (*C. auris*, private sector hospitals, $n = 43$) median (IQR) = 68 (40–140)

Abbreviations: ICU = intensive care unit, NHLS = National Health Laboratory Service, IQR = interquartile range, HR = hazard ratio, CI = confidence interval.

Table 4. Studies reporting drug susceptibility/resistance of *C. auris*.

Author	Study design		Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Adam[18]	Retrospective cohort study	Single centre	09/2010-12/2016	Kenya	Tertiary	Hospitalized patients with at least one *Candida*-positive blood culture within the study period	77	224	Blood
Adams[19]	Case series	Multi-centre	05/2013-04/2017	USA	Tertiary	Case-patient = person for whom a culture was positive for *C. auris*; Contact = person who had an epidemiological link to a case-patient in place or time	51	51 Case-patients 61 Contacts	Various sites
Ahmad[20]	Case series	Multi-centre	05/2014-12/2018	Kuwait	Tertiary	Hospitalized patients undergoing fungal infection workup	126	314	Various sites (including blood 58, urine 124, sputum/ET aspirate 91)
Alfouzan[21]	Case series	Single centre	01/2018-06/2019	Kuwait	Secondary	Secondary-care hospital in patients who yielded *C. auris* from bloodstream or other site in study period	17	151	Various sites (including urinary tract 50, blood 23, axilla 35, groin 25, trachea 8, nares 8, and central venous catheter 2
Al-Rashdi[22]	Case series	Multi-centre	01/2019-12/2019	Oman	Tertiary	Symptomatic and screened hospital in patients with positive *C. auris* isolate	108	129 Total; 16 Screening samples; 113 Clinical samples	Blood 44, urine 41, respiratory 9, CVC 9, wound 7, other 3, and unknown 16
Lockhart[8]	Case series	Multi-centre	2008, 2012-2015	Pakistan India South Africa Venezuela Japan	Tertiary	Hospital patients with positive *C. auris* isolate	41	54	Blood 27, urine 10, soft tissue 5, and other 12
Magobo[37]	Case series	Multi-centre	01/2012-12/2015	South Africa	Tertiary	Patients admitted to any South African hospital with first isolation of *C. auris* from any specimen	77	85	Urine, blood, CVC tips, irrigation fluid, tissue, respiratory tract specimens, and other
Chow[26]	Case series	Multi-centre	05/2013-08/2017	USA	Tertiary	Hospitalized patients (clinical cases) and screened contacts (screening cases)	73	385; 99 underwent AST	Blood, respiratory tract, urine, axilla, groin, nares, and wounds
Chowdhary[27]	Case series	Multi-centre	2009-2017	India	Tertiary	Tertiary hospital patients with *C. auris* candidaemia, invasive *C. auris* or colonization	n/a	350	Blood 267, tissue 25, pus 6, pericardial fluid 1, urine 28, sputum 12, skin swabs 9, faeces 1, and ear canal 1

Table 4. Continued

Author	Study design		Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Escandón[28]	Case series	Multi-centre	09/2016-05/2017	Colombia	Tertiary	Hospitalized patients with positive *C. auris* result	123	123	Blood 74, urine 11, respiratory specimens 10, GIT 7, other body fluids/sites 8, and unknown 13
Eyre[29]	Case control study	Multi-centre	02/2015-08/2017	England	Tertiary	Neurosciences ICU patients	66	n/a	Nose, axilla, groin, tracheostomy, wounds, urine, and blood
Garcia-Bustos[30]	Retrospective cohort study	Single centre	03/2016-03/2019	Spain	Tertiary	Patients previously colonized with *C. auris* admitted to surgical, medical, and burn ICUs	37	n/a	Blood, rectum, urine, respiratory tract, skin, and oropharynx
Govender[31]	Case series	Multi-centre	10/2012-11/2016	South Africa	Tertiary	Patients admitted to any South African healthcare facility with a positive *C. auris* culture	451	n/a	Blood 344, fluid (unspecified) 56, tissue 49, CSF 2, urine 622, CVC tips 288, respiratory tract 173, and skin/mucosa/wound 45
Zhu[52]	Case series	Multi-centre	08/2016-12/2018	USA	Tertiary	Health-care facility patients in New York with *C. auris* isolate in study period	277	413 infected; 966 underwent AST	Various sites (including blood (51%), urine (23%), and other)
Khan[32]	Case series	Multi-centre	05/2014-09/2017	Kuwait	Tertiary	Patients admitted to ICUs or other wards with positive *C. auris* isolate	56	158	Various sites (including blood 16, urine 53, and tracheal aspirate 51)
Kohlenberg[33]	Case series	Multi-centre	2013-2017	Spain, UK, Germany, France, Belgium, and Norway	Tertiary	Any patients with positive *C. auris* isolates	620	n/a	n/a
Kordalewska[34]	Case series	Multi-centre	n/a	India 40, Colombia 56, and USA 10	Tertiary	n/a	n/a	106	n/a
Kwon[35]	Case series	Multi-centre	1996-2018	Korea	Tertiary	Hospitalized patients with positive *C. auris*	61	61	Blood, ear swab
Pacilli[38]	Cross sectional study	Multi-centre	05/2016-12/2018	USA	Tertiary	Patients in healthcare facilities in Illinois with positive *C. auris* culture or PCR	128	n/a	Blood, urine, respiratory specimens, wound swabs, tissue, unknown, and axillary/groin swabs
Plachouras[40]	Case series	Multi-centre	01/2018-05/2019	Spain 291, UK 48, Germany 3, Netherlands 2, Austria 1, France 1, Greece 1, Norway 1, and Poland 1	Tertiary	Hospital patients with positive *C. auris* results	349	n/a	Blood 84, other 265

Table 4. Continued

Author	Study design	Study period	Country	Level of care	Population description	Number of patients	Number of isolates	Samples collected from
Rudramurthy[41]	Prospective cohort study	Multi-centre 04/2011-09/2012	India	Tertiary	ICU patients who acquired candidaemia in ICU	74	74	Blood
Ruiz-Gaitan[44]	Case series	Single centre n/a	Spain	Tertiary	Patients with positive *C. auris* isolate	n/a	73	Blood 56, urine 17
Sayeed[46]	Retrospective cohort study	Single centre 09/2014-04/2017	Pakistan	Tertiary	Hospitalized patients with positive *C. auris* culture	65	193	Blood 75, urine 83
Schelenz[48]	Case series	Single centre 04/2015-07/2016	England	Tertiary	Hospitalized patients with positive *C. auris* isolate	22	n/a	Wound swabs, urine, vascular device tips, blood, skin screening (nose, axilla, groin, and stool)
van Schalkwyk[51]	Retrospective cohort study	Multi-centre 01/2016-12/2017	South Africa	Tertiary	Patients who had *Candida* species blood specimen processed by an NHLS or private-sector laboratory	794	n/a	Blood

Abbreviations: AST = antifungal susceptibility testing, ET = endotracheal, CSF = cerebrospinal fluid, CVC = central venous catheter, GIT = gastrointestinal track, ICU = intensive care unit, PCR = Polymerase Chain Reaction, n/a = not available, NHLS = National Health Laboratory Service.

cially when other antifungals have been ineffective.[53] Potential *in vitro* and *in vivo* synergies between antifungal drugs should be evaluated to optimize the current treatment regimens against *C. auris*. The lack of mycology laboratory capacity for diagnosis, and for antifungal susceptibility testing (AFST) is a major challenge in many limited resource settings. The presence of various methods for antifungal susceptibility testing (AFST) with different robustness and unestablished clinical breakpoints poses another challenge in MICs interpretation and inter-method comparisons.[83,87] Reliable and standardized antifungal susceptibility testing methods are needed. Even access to such testing is also needed for widespread implementation in routine microbiology laboratories, especially in LMICs. Although *C. auris* has emerged more than 10 years ago, formal MIC breakpoints are still not available. Its relatively recent discovery and the existence of distinct clades with variations in susceptibility to antifungal agents[8] make it difficult to accumulate sufficient clinical data to inform breakpoints.[23] This may be further complicated by inconsistencies in susceptibility testing methods and results, probably resulting from the misidentification of *C. auris*, and lack of standards and guidance.[56] These challenges might complicate the clinical management of infections caused by *C. auris* because it is more challenging to interpret susceptibility testing results and select the most appropriate antifungal therapy. As a result, treatment often relies on expert opinion, and the clinical judgement of infectious disease specialists. The absence of breakpoint also impedes the understanding of antifungal resistance (AFR) and its burden (e.g., echinocandins—the antifungal most commonly used against *C. auris*). Therefore, this may present a challenge for optimized treatment, patient outcomes, and AFR mitigation. Collaborative efforts among researchers, clinicians, and public health agencies are essential for gathering comprehensive data on *C. auris* susceptibility patterns and establishing specific MIC breakpoints. Enhanced surveillance programmes focused on *C. auris*, coupled with standardized reporting mechanisms, can facilitate the timely detection of resistance trends and inform the development of new antifungal agents. This knowledge gap highlights the limited funding and calls for more investment in research and in building the laboratory capacity for *C. auris* detection and susceptibility testing to inform patient care and knowledge. CLSI and EUCAST, pivotal in antimicrobial susceptibility testing, offer standardized methodologies and interpretative guidance for testing practices, aiding in treatment decisions despite the absence of specific breakpoints for *C. auris*. Their interim recommendations and support for research and surveillance efforts help bridge the gap until more comprehensive data are available, contributing to the accurate assessment and optimization of antimicrobial therapy against emerging pathogen.

As an alert, pan-resistant isolates, i.e., those with resistance to all three classes of commonly prescribed antifungals: triazoles, polyenes, and echinocandins, have been reported in the USA, South Asia, and Africa.[8,88] As far as authors are aware, no pan-resistance from South America has been reported. These pan-resistance cases highlight the importance of continued and widespread surveillance and reporting for *C. auris*, appropriate antifungal prescribing (antifungal stewardship), and timely susceptibility testing on all clinical isolates. Optimal therapy for pan-resistant infections is unknown, and hence more research is needed.[88] It should be noted that data on *C. auris* drug resistance in LMICs was scarce due

Table 5. Susceptibility/resistance of *C. auris* to azoles.

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Adam[18]	Vitek2 AST-Y07	MIC ≤ 1: 0; MIC 2–8: 0 ; MIC 16–32: 18; MIC ≥ 64: 54				MIC ≤ 0.5: 10; MIC 1: 47; MIC ≥ 2: 5
Adams[19]	Custom Sensititre YeastOne panel; Amphotericin B and 5-flucytosine by Etest	R: 50/51, 98% ; Range: 8–≥ 256				
Ahmad[20]	Etest	Range: 32–256; MIC50: 256; MIC90: 256; MIC mean, SD: 246.4, 30.5; R: 314/314, 100%				Range: 0.023–6; MIC50: 1.5 MIC90: 3; MIC mean, SD: 1.2, 0.9; R: 107/260, 41.1%,
Alfouzan[21]	EUCAST	Candidaemia: MIC mean: 61.29; R: 14/16, 88% Colonized: R: 40/46, 87%; MIC mean: 51.83		Candidaemia: R: 14/16, 88%; MIC mean: 2.59 Colonized: R: 18/46, 39%; MIC mean: 0.36	Candidaemia: R: 1/16, 6%; MIC mean: 0.39 Colonized: R: 1/46, 2%; MIC mean: 0.02	Candidaemia: R: 15/16, 94%; MIC mean: 2.95 Colonized: R: 13/46, 28%; MIC mean: 0.27
Al-Rashdi[22]	Vitek2 AST-YS07	MIC ≤ 8: 4/77, 5.2% MIC 16: 34/77, 44.2% MIC ≥ 32: 39/77, 50.6%				MIC ≤ 1: 68/77, 88.3%; MIC 2: 7/77, 9.1%; MIC ≥ 4: 2/77, 2.6%
Lockhart[8]	CLSI M27-A3	Range: 4–256; MIC50: 128; MIC90: 256; R: 50/54, 93%		Range: 0.125–2; MIC50: 0.5; MIC90: 1	Range: 0.06–1; MIC50: 0.5; MIC90: 1	Range: 0.03–16; MIC50: 2; MIC90: 8; R: 29/54, 54%
Magobo[37]	Sensititre YeastOne; Etest for Isavuconazole	MIC50: 128; MIC90: 256; R: 82/85, 97%	MIC50: 0.019; MIC90: 0.38	MIC50: 0.03; MIC90: 0.12	MIC50: 0.015; MIC90: 0.06	MIC50: 0.12; MIC90: 1; R: 6/85, 7%
Chow[26]	CLSI; Etest for Amphotericin B	R:88/99, 89%				
Chowdhary[27]	CLSI M27-A3 (350 isolates)	Range: 1–≥ 64; MIC mean: 43.2; MIC50: 64; MIC90: 64	Range: ≤ 0.016–4; MIC mean: 0.07; MIC50: 0.03; MIC90: 0.5	Range: 0.03–16; MIC mean: 0.12; MIC50: 0.125; MIC90: 0.5	Range: ≤ 0.016–8; MIC mean: 0.05; MIC50: 0.03; MIC90: 0.125	Range: 0.03–16; MIC mean: 0.31; MIC50: 0.25; MIC90: 2
Escandón[28]	CLSI M27-A3; Etest for amphotericin B	R:28/93, 30%				
Eyre[29]	Sensititre YeastOne	R:79/79, 100%			R: 66/73, 90%	R: 78/80, 98%

Table 5. Continued

Author	MIC method	Fluconazole	Isavuconazole	Itraconazole	Posaconazole	Voriconazole
Zhu[52]	CLSI	First clinical isolate from 277 patients MIC90: > 256 R: 276/277, 99% Subsequent clinical isolate from 74 clinical patients MIC90: > 256 R: 116/116, 100%	First clinical isolate from 277 patients MIC90: 1 Subsequent clinical isolate from 74 clinical patients MIC90: 1	First clinical isolate from 277 patients MIC50: 0.5; MIC90: 1; Range: 0.12–1 Subsequent clinical isolate from 74 clinical patients MIC50: 0.5; MIC90: 1; Range: 0.12–1	First clinical isolate from 277 patients MIC50: 0.25; MIC90: 0.5; Range: 0.03–1 Subsequent clinical isolate from 74 clinical patients MIC50: 0.25; MIC90: 0.5; Range: 0.03–0.5	First clinical isolate from 277 patients MIC50: 2; MIC90: 2 Range: 0.25–4; R: 224/277, 81% Subsequent clinical isolate from 74 clinical patients MIC50: 2; MIC90: 2; Range: 0.5–4; R: 96/116, 83%
Khan[32]	Etest	MIC50: ≥ 256; MIC90: ≥ 256; Range: 128–≥ 256 MIC mean, SD: 252.8, 17.25; R: 56/56, 100%				MIC50: 1.5; MIC90: 3; Range: 0.064–6; MIC mean, SD: 1.20, 1.06; R: 41/56, 73.2%
Kwon[35]	CLSI M27-A3, Vitek2 AST-YS07	CLSI: R: 38/61, 62.3% Vitek2: R: 38/61, 62.3%				CLSI R: 0/61, 0% Vitek2 R: 0/61, 0%
Rudramurthy[41]	CLSI M27-A3	MIC mean: 29.36 MIC50: 64.0 MIC90: > 64		MIC mean: 0.08 MIC50: 0.06 MIC90: 0.25	MIC mean: 0.10 MIC50: 0.12 MIC90: 0.25	MIC mean: 0.36; MIC50: 0.50; MIC90: 2
Ruiz-Gaitan[44]	EUCAST, Sensititre YeastOne, MTS	MIC90:EUCAST > 64; SYO > 256; MTS > 256MIC mean:EUCAST > 64; SYO > 256; MTS 256	MIC90: EUCAST 0.12; MTS 0.25 MIC mean: EUCAST 0.066; MTS 0.117	MIC90: EUCAST 0.25; SYO 0.5 MIC mean: EUCAST 0.157; SYO 0.149	MIC90: EUCAST 0.12; SYO 0.125; MTS 0.5MIC mean: EUCAST 0.053; SYO 0.057; MTS 0.201	MIC90: EUCAST 4; SYO 4; MTS 64 MIC mean: EUCAST 2; SYO 1.7; MTS 52.43
Sayeed[46]	Sensititre YeastOne, Etest	R: 63/63, 100%		Tested 28 isolates but not reported	Tested 28 isolates but not reported	R: 18/63, 28.6%
Schelenz[48]	Not stated	Range: > 256				

Note: Data are reported as they appear in source documents. Susceptibility is expressed as mg/l unless indicated otherwise.
Abbreviations: R = resistant, S = susceptible, MIC = minimum inhibitory concentration, MIC50 = MIC required to inhibit the growth of 50% of isolates, MIC90 = MIC required to inhibit the growth of 90% of isolates, CLSI = Clinical and Laboratory Standards Institute, EUCAST = European Committee on Antimicrobial Susceptibility Testing. All studies used tentative breakpoints published by the US Centers for Disease Control and Prevention or epidemiological cutoff values.

Table 6. Susceptibility/resistance of *C. auris* to other antifungal drugs.

Author	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine	Nystatin	Terbinafine
Adam[18]	Vitek2 AST-Y07 ($n = 72$ *C. auris* isolates)		MIC ≤ 0.25: 20 MIC 0.5: 14 MIC ≥ 1: 0					
Adams[19]	Custom Sensititre YeastOne panel; Amphotericin B and 5-flucytosine by Etest	R: 0/51, 0% MIC50: 0.250 Range: 0.12–0.50	R: 0/51, 0% MIC50: 0.060 Range: 0.03–0.25	R: 0/51, 0% MIC50: 0.120 Range: 0.06–0.25	R: 15/51, 29% MIC50: 1.50 Range: 0.50–4.00			
Ahmad[20]	Etest			R: 3/169, 1.7% MIC90: 0.25 MIC mean, SD: 0.12, 0.8	R: 85/314, 27.1% MIC90: 2 MIC mean, SD: 1.2, 3.1	R: 0/137, 0% MIC90: 0.064 MIC mean, SD: 0.02, 0.08		
Alfouzan[21]	EUCAST	Candidaemia R: 0/16, 0% MIC mean: 0.02 Colonized R: 2/46, 4% MIC mean: 0.03	Candidaemia R: 12/16, 75% MIC mean: 2.18 Colonized R: 20/46, 43% MIC mean: 1.22	Candidaemia R: 0/16, 0% MIC mean: 0.02 Colonized R: 2/46, 4% MIC mean: 0.02	Candidaemia R: 0/16, 0% MIC mean: 0.71 Colonized R: 0/46, 0% MIC mean: 0.66			
Al-Rashdi[22]	Vitek2 AST-YS07		MIC ≤ 1: 76/77, 98.7% MIC 1: 0/77, 0% MIC ≥ 2: 1/77, 1.3%	MIC ≤ 1: 75/77, 97.4% MIC 2: 0/77, 0% MIC ≥ 4: 2/77, 2.6%	MIC ≤ 1: 3/77, 3.9% MIC 1: 9/77, 11.7% MIC ≥ 2: 65/77, 84.4%	MIC ≤ 8: 70/77, 90.9% MIC 16: 1/77, 1.3% MIC ≥ 32: 6/77, 7.8%		
Lockhart[8]	CLSI M27-A3	Range: 0.125–16 MIC50:0.5 MIC90: 1 R: 2/54, 4%	Range: 0.03–16 MIC50: 0.25 MIC90: 1 R: 2/54, 4%	Range: 0.06–4 MIC50: 0.25 MIC90: 2 R: 0/54, 0%	Range: 0.38–4 MIC50: 1 MIC90: 2 R: 19/54, 35%	Range: 0.125–128 MIC50: 0.125 MIC90: 0.5 R: 3/54, 6%		
Magobo[37]	Sensititre YeastOne; Etest for Isavuconazole	MIC50: 0.03 MIC90: 1 R: 1/85, 1%	MIC50: 0.06 MIC90: 2	MIC50: 0.06 MIC90: 2 R: 7/85, 8%	MIC50: 0.5 MIC90: 1 R: 0/85, 0%	MIC50: 0.06 MIC90: 0.12 R: 0/85, 0%		
Chow[26]	CLSI M27A-3; Etest for Amphotericin B	Echinocandins (not specified) R: 6/99, 6%			R: 33/99, 33%			
Chowdhary[27]	CLSI M27-A3 (350 isolates)	Range: <0.016–8 MIC mean: 0.27 MIC90: 1	Range: 0.125–16 MIC mean: 0.96 MIC90: 2	Range: < 0.016–16 MIC mean: 0.11 MIC90: 0.25	Range: 0.125–8 MIC mean: 0.74 MIC90: 1	Range: 0.125–≥ 64 MIC mean: 0.51 MIC90: 64	Range: 2–8 MIC mean: 3.1 MIC90: 4 (80 isolates)	Range: 2–32 MIC mean: 14.7 MIC90: 32 (110 isolates)

Table 6. Continued

Author	MIC method	Anidulafungin	Caspofungin	Micafungin	Amphotericin B	Flucytosine	Nystatin	Terbinafine
Escandón[28]	CLSI M27-A3; Etest for amphotericin B	R: 1/93, 1%			R: 20/93, 22%			
Eyre[29]	Sensititre YeastOne			R: 0/77, 0%	R: 14/79, 18%	R: 0/79, 0%		
Zhu[52]	CLSI M27-A3	First clinical isolate from 277 patients R: 0/277, 0% Subsequent clinical isolate from 74 patients R: 3/116, 2.6%		First clinical isolate from 277 patients R: 0/277, 0% Subsequent clinical isolate from 74 patients R: 4/116, 3.4%	First clinical isolate from 277 patients R: 170/277, 61% Subsequent clinical isolate from 74 patients R: 67/116, 58%	First clinical isolate from 277 patients R: 2/277, 0.7% Subsequent clinical isolate from 74 patients R: 6/116, 5.1%		
Khan[32]	Etest		MIC90: 0.38 MIC mean, SD: 0.19, 0.53 R: 1/56, 1.8%	MIC90: 0.125 MIC mean, SD: 0.093, 0.524 R: 1/56, 1.8%	MIC90: 2 MIC mean, SD: 1.05, 0.74 R: 13/56, 23.21%			
Kordalewska[34]	CLSI M27-A3	24 hours MIC90: 1 48 hours MIC90: 1	24 hours MIC90: 0.5 48 hours MIC90: >16	24 hours MIC90: 0.5 48 hours MIC90: 1				
Kwon[35]	CLSI M27-A3, Vitek2 AST-YS07		CLSI R: 0/61, 0% Vitek2 R: 0/61, 0%	CLSI R: 0/61, 0% Vitek2 R: 0/61, 0%	CLSI R: 0/61, 0% Vitek2 R: 0/61, 0%			
Rudramurthy[41]	CLSI M27-A3	MIC mean: 0.16 MIC50: 0.12 MIC90: 0.5	MIC mean: 0.80 MIC50: 1.0 MIC90: 2	MIC mean: 0.12 MIC50: 0.12 MIC90: 1	MIC mean: 0.52 MIC50: 1.0 MIC90: 2			
Ruiz-Gaitan[44]	EUCAST, Sensititre YeastOne, MTS	MIC90: EUCAST 0.06; SYO 0.25; MTS 0.125 MIC mean: EUCAST 0.035; SYO 0.121; MTS 0.051		MIC90: EUCAST 0.06; SYO 0.06; MTS 0.064 MIC mean: EUCAST 0.052; SYO 0.057; MTS 0.031	MIC90: EUCAST 0.25; SYO 0.5; MTS 2 MIC mean: EUCAST 0.136; SYO 0.38; MTS 0.407			
Sayeed[46]	Sensititre YeastOne, Etest	R: 0/28, 0%	R: 0/28, 0%	R: 0/28, 0%	R: 5/63, 7.9%			
Schelenz[48]	Not stated	Range: (echinocandins, not specified) 0.06-0.25			Range: 0.5–2	Range: < 0.06–0.12		

Data are reported as they appear in source documents. Susceptibility is expressed as mg/l unless indicated otherwise.
Abbreviations: CLSI = Clinical and Laboratory Standards Institute, EUCAST = European Committee on Antimicrobial Susceptibility Testing, R = resistant, S = susceptible, SD = standard deviation, SYO = Sensititre YeastOne, MIC = minimum inhibitory concentration, MTS = MIC Test Strip, MIC50 = MIC required to inhibit the growth of 50% of isolates, MIC90 = MIC required to inhibit the growth of 90% of isolates. All studies used tentative breakpoints published by the US Centers for Disease Control and Prevention. All MIC values given in mg/l or μg/ml.

Table 7. Risk factors for developing *C. auris* infection.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Total number of patients	Number of patients infected by *C. auris*	Risk factors	Impact of risk factors
Adam[18]	2019	Retrospective cohort study	Single centre	09/2010-12/2016	Kenya	Tertiary	Hospitalized patients with at least one *Candida*-positive blood culture	201	77	Renal failure before admission CCU admission Mechanical ventilation CVC presence	OR (95%CI) 2.31 (1.13-4.75)—*C. auris* vs. other candida OR (95%CI) 2.76 (1.26-6.06)—*C. auris* vs. *C. albicans* OR (95%CI) 3.17 (1.17-8.57)—*C. auris* vs. other candida OR (95%CI) 4.61 (2.01-10.58)—*C. auris* vs. *C. albicans*
Caceres[25]	2020	Case control study	Multi-centre	01/2015-09/2016	Colombia	Tertiary	Patients with *C. auris* candidaemia or non-*C. auris* candidaemia (excluding *C. haemulonii*, *C. sake*, and *Candida* spp. due to potential for misidentification as *C. auris*)	90	40	Diabetes (*C. auris* candidaemia vs. non-*C. auris* candidaemia) ≥15 days of pre-infection ICU stay Haemodialysis in hospital Evidence of severe sepsis	OR (95%CI) 4.94 (1.09-22.3) OR (95%CI) 5.11 (2.01-13.0) OR (95%CI) 3.52 (1.25–9.91) OR (95%CI) 3.47 (1.27–9.48)
Eyre[29]	2018	Case control study	Multi-centre	02/2015-08/2017	England	Tertiary	Neurosciences ICU patients	427	66	3 day ICU stay before diagnosis 5 day ICU stay before diagnosis 10 day ICU stay before diagnosis Axillary temperature monitoring used Neutrophil count 4000–7000 cells/mm^3 Neutrophil count 7000–10000 cells/mm^3	OR, 95%CI 2.24, 1.30-3.86 OR, 95%CI 2.97, 1.35-6.53 OR, 95%CI 2.78, 1.02-7.54 OR, 95%CI 6.80, 2.96-15.63 OR, 95%CI 2.21, 1.30-3.76 OR, 95%CI 4.72, 1.64-13.59

Table 7. Continued

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Total number of patients	Number of patients infected by *C. auris*	Risk factors	Impact of risk factors
Garcia-Bustos[30]	2020	Retrospective cohort study	Single centre	03/2016-03/2019	Spain	Tertiary	Patients previously colonized with *C. auris* admitted to surgical, medical, and burn ICUs	206	37	Total parenteral nutrition Previous surgery Sepsis Previous exposure to antifungal agents Arterial catheters Central venous catheters Advanced chronic kidney disease Multifocal colonization	adjusted OR 3.73 aOR 1.03 aOR 1.75 aOR 1.17 aOR 1.46 aOR 1.21 aOR 1.35 aOR of unifocal colonization 0.46
Rudramurthy[41]	2017	Prospective cohort study	Multi-centre	04/2011-09/2012	India	Tertiary	ICU patients who acquired candidaemia in ICU	74	74	*Candida auris* vs. non-*C. auris* Public-sector hospital Northern India ICUs Underlying respiratory disease Urinary catheter Vascular surgery Prior antifungal exposure (especially azoles, followed by echinocandins) APACHE II at admission	OR (95%CI) 2.2 (1.25-3.87) OR (95%CI) 2.1 (1.17-3.84) OR (95%CI) 2.1 (1.31-3.60) OR (95%CI) 1.9 (1.11-3.42) OR (95%CI) 2.3 (1.00-5.36) OR (95%CI) 2.8 (1.64-4.86) OR (95%CI) 0.8 (0.81-0.96)
Ruiz-Gaitan[42]	2019	Case control study	Single centre	04/2016-02/2017	Spain	Tertiary	Patients admitted to surgical ICU or medical ICU	228	41	Case vs. control (case = colonization or candidaemia) Indwelling CVC (OR, 95%CI) Parenteral nutrition (OR, 95%CI) Mechanical ventilation (OR, 95%CI)	13.48, 3.85-47.53 3.49, 1.82-6.69 2.43, 1.24-4.75

Table 7. Continued

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Total number of patients	Number of patients infected by *C. auris*	Risk factors	Impact of risk factors
Sayeed[47]	2020	Retrospective cohort study	Single centre	09/2014-03/2017	Pakistan	Tertiary	Patients age > 16 with candidaemia	138	37	*Candida auris* candidaemia vs. non-*C. auris*: Prior history of surgery Antifungal use in the last 90 days Isolation of multi-drug resistant bacteria before isolating candida	Adjusted OR, 95%CI (p-value) 4.9, 1.4-17.5 (0.012) 38.3, 4.1-356.8 (0.001) 5.09, 1.6-15.9 (0.005)
Shastri[49]	2020	Prospective cohort study	Single centre	04/2016-09/2017	India	Tertiary	Patients developing candidaemia 48 hours after ICU admission	108	42	*Candida auris* candidaemia vs. non-*C. auris* candidaemia Underlying respiratory illness Underlying neurological illness	OR, 95%CI (p-value) 5.34, 1.43-19.85 (0.012) 5.30, 1.18-23.81 (0.029)
van Schalkwyk[51]	2019	Retrospective cohort study	Multi-centre	01/2016-12/2017	South Africa	Tertiary	Patients who had *Candida* species blood specimen processed by an NHLS or private-sector laboratory	5876	794	Prior systemic antifungal therapy (especially azoles) CVC in situ Admission to private-sector facility Older age (per year) Longer hospitalization prior to first positive blood culture (per day admitted)	aOR, 95%CI 1.4, 0.8-2.3 aOR, 95%CI 1.8, 1.05-3.01 aOR, 95%CI 2.7, 1.4-4.7 aOR, 95%CI 1.01, 1.01-1.03 aOR, 95%CI 1.01, 1.01-1.02

Abbreviations: ICU = intensive care unit, NHLS = National Health Laboratory Service, CCU = critical care unit, CVC = central venous catheter, OR = odds ratio, aOR = adjusted odds ratio, CI = confidence interval.

Table 8. Distribution and incidence/prevalence of *C. auris*.

Author	Year	Study design	Study design	Study period	Country	Level of care	Population description	Total number of patients	Number of patients infected by *C. auris*	Prevalence
Adam[18]	2019	Retrospective cohort study	Single centre	09/2010-12/2016	Kenya	Tertiary	Hospitalized patients with at least one *Candida*-positive blood culture	201	77	2011 12/34, 35% 2012 20/37, 54% 2013 19/41, 46% 2014 14/26, 54% 2015 8/29, 28% 2016 4/36, 11%
Pacilli[38]	2020	Cross sectional study	Multi-centre	05/2016-12/2018	USA	Tertiary	Patients in healthcare facilities in Illinois with positive *C. auris* culture or PCR result	490	128	Highest prevalence of *C. auris* colonization in vSNF settings (prevalence, 23–71%) during 2016–2018. Increasing *C. auris* prevalence from 43% to 71% during 2018 in one vSNF.
Rudramurthy[41]	2017	Prospective cohort study	Multi-centre	04/2011-09/2012	India	Tertiary	ICU patients who acquired candidaemia in ICU	74	74	74 cases *C. auris*/1400 cases total candidaemia (5.3%) in 27 ICUs from 04/2011-09/2012
Shastri[49]	2020	Prospective cohort study	Single centre	04/2016-09/2017	India	Tertiary	Patients developing candidaemia 48 hours after ICU admission	108	42	*Candida auris* 42 cases/108 candidaemia cases = 38.9%, Incidence: 6.75/1000 ICU bed days
van Schalkwyk[51]	2019	Retrospective cohort study	Multi-centre	01/2016-12/2017	South Africa	Tertiary	Patients who had *Candida* species blood specimen processed by an NHLS or private-sector laboratory	5876	794	Among 6669 cases (5876 with species identification) from 269 hospitals, 794 (14%) were caused by *C. auris*. Cases/100 000 hospital admissions: 12.50, 95%CI 11.5–13.6)

Abbreviations: ICU = intensive care unit, PCR = Polymerase Chain Reaction, NHLS = National Health Laboratory Service, CI = confidence interval, vSNF = ventilator-capable skilled nursing facility.

to the limited capacity for AFST in routine practice.[89] Laboratory capacity in these countries needs to be enhanced and/or supported to ensure the appropriate use of antifungals and to reduce the risk of developing resistance. Regional-specific treatment guidelines should also be established, given the diverse resistance patterns and resources around the world.[89]

Candida auris is globally distributed. During the last 10 years, outbreaks, or invasive healthcare-associated infections due to *C. auris* were frequently reported in many countries. Given the difficulty in identifying *C. auris* isolates with conventional phenotypic methods, the real incidence of *C. auris* isolates is likely underestimated, especially in LMICs where resource for species identification are limited.[89] Global trends could not be fully assessed due to the lack of data from the included studies, only one country from Africa (Kenya), and the USA reported increasing trends. According to the Pan American Health Organization (PAHO)/WHO, an overall increase in *C. auris* infection was observed, especially during the COVID-19 pandemic in the WHO region of the Americas.[6] Cases in the USA in 2018 increased by 318% compared with the average percentage of reported cases during 2015–2017.[90] In 2020, four countries in the Central and Southern America (Brazil, Guatemala, Mexico, and Peru) reported the first cases for the first time.[6]

Our review has several limitations. First, publication bias might have occurred as our research did not retrieve studies from LMICs regarding epidemiology and antifungal resistance. Possible explanations are that these studies did not exist, were published in a language other than English, or were not included in databases and only disseminated locally. Second, the selection bias of our search cannot be ruled out due to the inclusion of only two databases. Third, the impact of the COVID-19 pandemic on *C. auris* infections could not be assessed, as only papers published by February 2021 were included. Considering these limitations, we interpreted the results with caution. Although we excluded studies published before 2011, studies published between the discovery in 2009 and 2011 would likely not have affected the assessment of the outcome criteria as at that time little was known about the pathogen.

The inclusion of *C. auris* as a critical priority pathogen in the WHO FPPL underscores its significance as a global health threat. The high mortality rates associated with *C. auris* infections, coupled with its multidrug-resistant nature and ability to cause outbreaks, necessitate urgent collaborative efforts to develop effective prevention, surveillance, and treatment strategies.

Several key research directions should be considered in the context of *C. auris* infections. Exploring novel treatment options, understanding the genetic and virulence factors contributing to variability in clinical outcomes, evaluating the effectiveness of infection prevention and control measures, and establishing standardized methods for antifungal susceptibility testing are all areas that warrant further investigation.

An adequate management of *C. auris* infections requires a multidisciplinary approach involving infectious disease specialists, microbiologists, infection control teams, and healthcare administrators. There are no regulatory protocols for decolonization, as data on the efficacy of decolonization for patients with *C. auris* are unavailable. However, fundamental guidance on infection control should be followed such as isolating these patients during their hospitalization stay, establishing transmission-based precautions, and continuing hand hygiene and PPE practices.[7,73,91] The challenges posed by this emerging pathogen can only be effectively addressed through coordinated efforts, early detection, appropriate management, and continuous research.

Conclusion

Mortality associated with *C. auris* infection is high, especially in those critically ill, diagnosed with *C. auris* candidaemia, kidney disease, or who underwent invasive procedures. Resistance to fluconazole was high and susceptibility to other azoles varied across the studies. Moderate resistance rates to amphotericin B and lower ones to echinocandins were reported. Risk factors for developing *C. auris* infections include long ICU stay and ICU-related procedures, previous use of antifungals, previous use of broad-spectrum antibiotics, an underlying diagnosis of renal impairment, and multisite colonization. Interventions targeting these risk factors should be explored for their effectiveness and feasibility. Implementation of recommended infection prevention control measures in healthcare facilities is essential for prevention and control. *Candida auris* is globally distributed with an increasing trend in the last decade. Global surveillance studies could better inform the annual incidence rates, distribution, and AFS trends, in all countries and regions, especially in LMICs. Optimal management of patients infected or colonized by *C. auris* is unclear and warrants further study.

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Conflict of interest

The authors have no conflicts of interest to declare.

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