Review Article

# A Review of Epidemiology and Antifungal Susceptibility of non-Candida albicans species in Iran

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## Abstract

**Background:** Candidiasis is among the most widespread infections caused by fungi species. Although C. albicans still serves as the primary source of this infection, the occurrence and antifungal resistance of non-Candida albicans species seem to be increasing.
**Materials and Methods:** The data was gathered from multiple sources across Pubmed and Google Scholar using candidiasis, anti-fungal resistance, epidemiology, non-*Candida albicans* species, and Iran. Different types of articles from 2016 to 2024 regarding candidiasis in various regions of Iran and cases of resistant non-*Candida albicans* species were included.
**Results:** In this review article, we analyzed the susceptibility of non-*Candida albicans* species to multiple anti-fungal agents and observed variable resistance patterns to commonly used agents. However, fluconazole showed resistance more often than other agents, and amphotericin B showed the least amount of resistance overall.
**Conclusion:** This study aimed to demonstrate the importance of geographical factors and causative species in Iran's resistance pattern and treatment of candidiasis. This can help medical practitioners prescribe the optimum therapeutic agent for candidiasis patients.
**Keywords:** Candidiasis, Antifungal agents, Drug resistance, Epidemiology, Iran

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## Introduction

Infection with *Candida* species, better known as Candidiasis, is an opportunistic fungal infection[1]. It first appears in the gastrointestinal tract, on the mucosal membranes, and on the skin and can further invade the body and affect multiple vital organs such as the brain, heart, bones, eyes, and other parts such as the blood. Over the past few years, reports of those infected have grown due to several epidemiologic and medical factors, such as the increase in leukemic patients, diabetes mellitus, and higher use of immunosuppressive drugs[2]. Even though *Candida albicans* remains the primary cause of candidiasis, the incidence of non-*Candida albicans* species (NCAS), such as *C. tropicalis*, *C. glabrata*, and *C. parapsilosis* has increased[3]. The surge in multidrug-resistant (MDR) NCAS, notably *C. auris, is* another concern[4].
In recent studies, these species have shown decreased susceptibility to several antifungal drugs, including echinocandins, azoles (especially fluconazole), and triazoles, making the treatment of this infection

challenging for many patients[4,5]. Adversely, most of the aforementioned causes of this infection rapidly become resistant to antifungal drugs or have intrinsically lower sensitivity to commonly used antifungal agents[1]. This highlights a significant contributing factor to drug resistance: the broad application of fluconazole prophylaxis in several patients[6]. Consequently, morbidity and mortality rates of NCAS have risen, making the management of this infection and choosing the best antifungal therapy essential[1]. In addition, the possibility of underlying diseases and the immune status must also be considered to determine the best therapeutic medicine for each patient[7]. Also, *Candida* species are spread differently worldwide due to the discrepancies between population characteristics, sampling protocols, and geographic zones. Hence, having a valuable data source regarding the most prevalent *Candida* species seems necessary[3].

Therefore, performing epidemiology-based studies exploring the distribution and resistance of *Candida* species in affected countries seems more essential than ever to further characterize patients' clinical profiles[4]. Ergo, this research aimed to study the prevalence of NCAS and their susceptibility pattern in Iran to find the best therapeutic option.

## Methods

This review article was conducted to illustrate the epidemiology of NCAS in Iran and their resistance to the commonly used antifungal drugs in different regions. Data on the resistance patterns seen in hospitals nationwide were acquired through a comprehensive search using two primary sources: Pubmed and Google Scholar. Multiple relevant articles and literature published between 2016 and 2024 were included, and non-English articles were excluded. The search strategy involved extracting data from sources containing keywords such as candidiasis, anti-fungal drugs, resistance, epidemiology, and Iran.

## Results

***Candida auris*:** Several studies have been conducted in Iran regarding the prevalence of candidemia and its causative agents. In this review, the epidemiology of NCAS has been analyzed. Despite the increasing prevalence of *C. auris* in the neighboring countries, there have been only ten confirmed cases of *C. auris* in Iran[8,9]. The primary type of infection among these cases was otomycosis, but other types, such as chronic mucocutaneous candidiasis and meningitis, have also been seen. These cases have been reported in cities such as Babol, Tehran, Isfahan, and Shiraz. Most of these cases belong to clade V of *C. auris*[9]. Studies on some of these cases are as follows: Ahmadi et al. reported an otomycosis case caused by *C. auris* in a seventy-eight-year-old man diagnosed with diabetes mellitus type II in 2017 with no epidemiological connection to travel history or other patients. Short tandem repeats genotyping analysis and Whole genome sequencing (WGS) showed that this sample consists of clade I of *C. auris*[10]. Another study described an immunocompetent patient diagnosed with *C. auris* otitis, the first fluconazole-resistant case of this condition in Iran. In August 2020, a 40-year-old woman with bilateral ear pain for three years, accompanied by creamy discharge and severe itching in the ear canal, was admitted to the Department of Otorhinolaryngology[11]. Research was done on patients in an intensive care unit (ICU) in Isfahan, Iran, to discover whether it is more likely to see colonization of *C. auris* in immunocompromised patients. Therefore, 32 immunocompromised patients admitted to ICU in the past 7 to 14 days were tested for *C. auris*[12]. In another research, 325 suspected cases admitted to 4 university hospitals (Amin, Imam Hossein, Seyed-al-Shohada, and Al-Zahra) were a part of this study based on clinical symptoms from April 2018 to June 2021. Patients without oncological or hematological treatment in the past year were excluded from the study[13].

***Candida tropicalis*:** In a study conducted by Jahanshiri Z et al., 116 head and neck cancer patients with oropharyngeal cancer (OPC) were examined, and thirty-eight *C. tropicalis* cases were detected among them at Imam Khomeini Hospital in Tehran, confirmed by the Ethics Committee of Pasteur Institute of Iran (IR.PII.REC.1398.052). A selection of patients of different sexes and ages who had undergone radiotherapy in the past two weeks was chosen[14]. In another study from 2014 to 2015 on patients from 10 university hospitals in Iran, 846 *Candida* species were

detected among more than 4000 potential cases examined. 74 of these 846 cases consist of *C. tropicalis*, which were isolated from blood, rectum, mouth, nose, bronchoalveolar lavage, vagina, and urine. The aforementioned university hospitals included Kerman, Isfahan, Ahvaz, Sanandaj, Mashhad, Shiraz, Sari, Yasuj, Tehran, and Urmia[15]. Sharifzadeh et al. reported that Twelve *C. tropicalis* (Ct1-Ct12) isolates, isolated from the uterus and vagina of mares, were extracted from their patients at different times[16]. In another research, 33 patients were examined before and during head-and-neck radiotherapy, and *Candida* species were isolated in Sayed-al-Shohada Hospital in Isfahan, Iran. These cases consisted of 15 men and 18 women at the beginning of the study (aged 38-74 years). Twenty-one of these patients tested positive for *Candida* infection before treatment. 19 out of 27 patients tested *Candida*-positive, and six patients expired (two women and four men) In the second week of radiotherapy. More than one *Candida* strain was detected in some patients, such as *C. tropicalis* and *C. albicans*[17]. In another research, 64 *C. tropicalis* blood samples gathered from candidemia patients referred to 10 different hospitals in three large cities of Iran (Shiraz, Tehran, and Mashhad) were included from September 2014 to February 2019. Patients had other underlying conditions and wards[18].

***Candida glabrata*:** It seems that *C. glabrata* is the second most common cause of candidiasis and, therefore, an important source of infection in individuals. A study by Zarrinfar et al. collected 189 vaginal discharge specimens from women suspicious of infection with vulvovaginal candidiasis (VVC). A total of 108 *Candida* isolates were gathered and later examined by Mashhad's University of Medical Sciences health centers. In the primary stage, the polymerase chain reaction-restriction fragment length polymorphism (PCR-LFP) method was used to identify *Candida* isolates. The results indicated that 15 isolates were *C. glabrata*[19]. From clinical laboratories in Tehran-Iran, fifty *C. glabrata* isolates were obtained. Strains were collected from various patients; however, the sites from which the samples were collected varied. Most samples were obtained from blood, followed by urine[20]. In a multicenter study from 2015 to 2018, sixty-five patients with a median age of fifty-eight years provided seventy *C. glabrata* isolates. Both male (52.3%) and female (47.7%) patients were examined. Blood samples were the main source of the isolates. Most of these patients were held in ICU, coronary care units, neonatal intensive care units (NICU), and pediatric intensive care units (PICU). Other hospital units, such as surgery, emergency, internal medicine, infectious diseases, pediatric, and general units for men, also contributed to the patient population[21]. In another study by Badiee et al., 2,385 clinical samples were obtained from patients exhibiting signs and symptoms of infections. From ten university hospitals (in Iran), 598 *Candida* isolates were acquired. Most of these specimens were obtained from the oral cavity. *C. glabrata* caused the most infections after *C. albicans*[22]. Nouri et al. investigated ICU wards from December 2017 to May 2018 and studied ninety patients hospitalized in teaching hospitals in Iran. Both male and female patients were above eighteen years of age and showed clinical symptoms of oral candidiasis. Swab samples were taken from the oral cavities, identifying 40 isolates as *C. glabrata*[23]. Regarding candidemia affecting immunocompromised patients, fifty-one acute myeloid leukemia (AML) patients hospitalized in the hematology-oncology ward of Valiasr Hospital (Tehran) participated in a study before antineoplastic treatment initiation. Samples were collected by gently rubbing a swab on the oropharynx and the dorsal surface of the tongue, twenty-one of which were positive for *Candida*[24].

***Candida parapsilosis*:** One of the most widespread yeasts associated with invasive *Candida* infection is *C. parapsilosis*. It is often isolated from individuals with compromised immune systems, particularly in pediatric units. Invasive candidiasis caused by *C. parapsilosis* has recently increased. In one study by Lotfali et al., epidemiological studies collected and diagnosed *C. parapsilosis* isolates previously recovered from 120 patients in Tehran, Isfahan, Mazandaran, and Alborz provinces between 2009 and 2013. 65% were female and 35% male, with a mean age of 42.4 years[25]. During a thirty-month study, from July 2014 to December 2016, in Tehran, 156 cases of invasive candidiasis were recognized in 149 patients. *C.parapsilosis* made up 24.4% of the spp. Isolates obtained from patients referred to ICUs[6]. Candidemia patients admitted to three hospitals in Shiraz, namely Faghihi,

Amirolmomenin, and Namazi, from 2016 to 2018, posed as study subjects, resulting in the recovery of 113 yeasts from 109 patients. The current study did not include neonates and infants. Invasive candidiasis or candidemia is diagnosed When blood cultures from other sterile body fluids, such as cerebrospinal fluid (CSF), yield yeast. *C. parapsilosis* is the third most widespread yeast identified (n=13)[26]. In another study, 1,770 *Candida* species were primarily recovered from blood during five years (2014- 2019) from the Tehran, Mashhad, and Shiraz clinical centers. This resulted in the collecting of 600 (33.8%) *C. parapsilosis* species complex isolates[27]. Another study by Davari et al. gathered patients with several clinical forms of *Candida* infection. A total of 105 clinical *C. parapsilosis* isolates were obtained from 2014–2017. All 105 isolates were *C. parapsilosis*. The stock cultures were preserved in the Invasive Fungi Research Centre (Sari, Iran)[28]. Another study conducted in Tehran hospitals (Imam Khomeini, Baqiyatallah, Shohadaye Tajrish) collected 40,412 blood samples. The culture of the samples started in February 2014 and concluded in March 2015. Of all isolates, 204 cases were yeast positive. These samples were collected from 125 male (53) and female (72) patients. The mean was 36.1 years for females and 20.7 years for males. The age range varied from 0-90 years. *C. parapsilosis* posed as the second most frequent *Candida* among the cultures[29]. Epidemiology and resistance of NCAS in different cities of Iran shows in Table 1.

**Table 1.** Epidemiology and resistance of NCAS in different cities of Iran

| NO. | study | region | No. centers | No. cases | species | Age /gender | site | Antifungal agent | Testing method | Resistance |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Kobrazadeh et al.[9] | Multiple (Tehran, Isfahan, Babol, etc.) | NM | 10 | *C. auris* | NM/M-F | Ear, meninges, mucus, and skin | FLC | NM | NM |
| 2 | Ahmadi et al.[10] | Bushehr | 1 | 1 | *C. auris* | 78y/M | Ear discharge | FLC, ITC, CAS, AMB Miconazole | KOH smear, CHROM agar *Candida* | Susceptible |
| 3 | Sharifi et al .[13] | Isfahan | 4 | 74 | *C. glabrata*, *C. tropicalis*, *C. parapsilosis* | 1-89y/M-F | Urine, BAL, blood | AMB, ITC, FLC, INN | PCR-RFLP | INN (17.6%) FLC (9.4%) ITC (5.4%) AMB (0%) |
| 4 | Nouri et al .[23] | NM | Multicenter | 40 | *C. glabrata* | 15-95y/M-F | Oral cavity | FLC, ITC, AMB, TQ | plex PCR | FLC (72.5%) ITC (12.5%) AMB (5%) |
| 5 | Jahanshiri et al.[14] | Tehran | 1 | 38 | *C. tropicalis* | NM/M-F | NM | FLC, VRC, ITC, AMB, CAS | multiplex PCR | CAS (23.68%) FLC (18.42%) AMB (13.15%) ITC (10.52%) VRC (5.26%) |
| 6 | Badiee et al.[22] | Multiple (Shiraz, | 10 | 125 | *C. glabrata* | NM/M-F | Oral cavity, BAL fluid, | CAS, VRC, AMB, | PCR-RFLP Sequencing | 53.6% multi-azole resistant. CAS (0.9%) |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | Mashhad, Isfahan, etc.) | | | | | anus, Blood, skin and nail, gastric juice | ISAV ITC, LLCZ, POS, FLC | | |
| 7 | Golestannejad et al.[17] | Isfahan | 1 | 21 | *C. glabrata*, *C. tropicalis*, *C. parapsilosis* | 38-74y/M-F | NM | FLC, VRC | PCR-RFLP | FLC (0%) VRC (0%) |
| 8 | Zarrinfar et al.[19] | Mashhad | NM | 15 | *C. glabrata* | NM/F | Vaginal discharge | VRC, ITC, FLC, KTZ | PCR-RFLP | FLC (67%) ITC (27%) VRC (0%) KTZ (0%) |
| 9 | Armaki et al.[11] | Babol, Sari | NM | 1 | *C. auris* | 40y/F | Ear discharge | FLC, VRC, ITC, Miconazole, AMB, POS, ISZ, Ravuconazole, KTZ, CLOT, Nystatin, MYC, INN | PCR | FLC (100%) CLOT and miconazole: improved |
| 10 | Arastehfar et al.[26] | Shiraz | 3 | 109 | *C. glabrata* *C. Tropicalis* *C. parapsilosis* | 1-89y/M-F | Blood, abdominal fluids, CSF, wound abscesses, liver abscesses, central venous catheter | FLC, AMB, ITC, VRC, POS | CHROM agar *Candida*, MALDI-TOF | FLC (2.1%) VRC (0%) ITC (NM) AMB (NM) POS (NM) |
| 11 | Sharifzadeh et al.[16] | Amol | 1 | 21 | *C. tropicalis* | NM/NM | Vagina, uterus | VRC | CHROM medium, PCR-RFLP | VRC (33.33%) |
| 12 | Davari et al.[28] | Sari | 1 | 105 | *C. parapsilosis* | NM/NM | various clinical forms | CAS, INN, MYC | NM | Echinocandins: CAS, INN, MYC (2.9%) |
| 13 | Arastehfar et al.[18] | Mashhad, Shiraz, Tehran | 10 | 64 | *C. tropicalis* | ۲ months to 90 years/ | blood | FLC, VRC, ITC, AMB, | MALDI-TOF AFLP fingerprinti | VRC (10.93%) FLC (6.25%) MYC (3.12%) ITC (3.12%) |

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|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | M-F | | MYC, INN | ng | INN (0%) AMB (0%) |
| 14 | Arastehfar et al.[21] | Multiple (Tehran, Isfahan, Shiraz, etc.) | NM | 70 | *C.glabrata* | 58/M-F | Blood, central venous catheters, and abdominal fluids | FLC, VRC, ITC, POS, CAS, AMB | plex PCR, MALDI-TOF AFLP, sequencing | CAS (57.7%) VRC (36.43%) FLC (1.4%) ITC (0%) AMB (0%) |
| 15 | Amanloo et al.[20] | Tehran | 1 | 50 | *C.glabrata* | NM/NM | NM | AMB, CAS, FLC, VRC | API 20C AUX, CHROMagar, PCR | FLC (8%) VRC (2%) AMB (0%) CAS (0%) |
| 16 | Lotfali et al.[25] | Multiple (Tehran, Isfahan, Mazandaran, Alborz.) | ٤ | 120 | *C.parapsilosis* | 6-81/M-F | Nail، Groin, Interdigital, Vaginitis, Hand, sputum, ear discharge | FLC, ITC, AMB, | CHROMagar, PCR-RFLP | ITC (2.5%) FLC (2%) AMB (2%) |

NM: not mentioned; M: male; F: female; FLC: fluconazole; ITC: itraconazole; CAS: caspofangin; AMB: amphotericin B; BAL: bronchoalveolar lavage; INN, anidulafungin; TQ: thymoquinone; VRC, voriconazole; ISAV: isavuconazole; LLCZ: luliconazole; POS: posaconazole; KTZ: ketoconazole; CLOT: clotrimazole; MYC: micafungin;

## Discussion

As previously stated, *Candida* infection is one of the most common fungal infections worldwide. Therefore, the growing resistance of its causative agents to commonly used antifungal medications causes concers[4,5]. In this review, the data surrounding the epidemiology and antifungal resistance of four NAC species was extracted from several studies conducted in Iran from 2016 to 2024. One of the main contributing factors to the increased rate of resistance is the potency of the immune system; therefore, in neonates and leukemic, ICU, diabetic, and immunosuppressed patients, a higher risk of infection and resistance can be seen[3,6,7,14]. In addition, geographical factors such as climate, regional customs, and the level of education seem to contribute to the prevalence of *Candida* infections. They can be taken into consideration for more preferable therapeutic outcomes[3]. The investigated articles considered these factors, resulting in a wide range of antifungal susceptibility among patients.

In one study conducted on neonates and pediatric patients admitted to ICU wards in Tehran, a 42.5% mortality rate was reported, emphasizing the immense impact of candidiasis on ICU patients[6]. NAC species were obtained from nearly half of the patients, necessitating further attention to causative agents of candidiasis and appropriate treatment despite the rising antifungal resistance.

In another study, a comparison between acute myeloid leukemia (AML) patients and healthy controls demonstrated significantly higher oral *Candida* colonization in AML patients, with a 72.5% prevalence against 25.8% in healthy controls[3]. This result underscores the higher resistance rate to commonly used antifungal agents in AML patients. Therefore, routine screening for oral candidiasis and continuous monitoring of antifungal resistance patterns seems crucial in optimizing therapeutic approaches in these patients.

The resistance to the tested antifungal drugs varied between these four species. However, a notable fact was the high resistance rate in patients treated with fluconazole (especially those with *C. glabrata* and *C. auris infection)* and the low resistance in those treated with amphotericin B.

Studies were conducted in different cities and locations in Iran, and the resistance pattern indicates the challenging issue of widespread antifungal resistance. Both male and female patients in a broad age group were included, showing a spectrum of populations at risk of resistance.

Another noticeable fact was the difference in the prevalence of these infections, with *C. glabrata* being the dominant species in almost every study[5]. *C. auris* appeared to be the rarest fungal agent, nevertheless showing the highest innate resistance to drugs due to being intrinsically MDR[10].

Concerning the drug resistance pattern, as said before, FLC seemed to be the least effective drug for treating C. glabrata, with a 72.5% resistance in a study on hospitalized patients and 67% in another research in Mashhad[19,25]. Nevertheless, resistance to FLC varied significantly, and other studies showed a 0-30% resistance to the drugs[4,5,13,14,17,20,21,25]. Other azoles also showed varying susceptibility rates. Namely, VRC showed a 0-36.5% resistance rate in studies, and ITC a rate of 0-27%[13,14,16-21,23,25,26]. Considering that azoles are the leading used drugs in empirical therapy, this broad antifungal resistance seems alarming.

In contrast, AMB was used in fewer studies and was proven effective, showing 0% resistance in most studies and 13.15% resistance at most, making it a proper choice of drug for resistant patients[13,14,18,20,21,23,25].

Echinocandines seem to be a proper alternative, given the lower rates of resistance varying from 0-57.7%[21]. However, INN seems to be a poor drug choice for C. Auris, with a 60% rate of resistance[13].

Based on the data in these research studies, the susceptibility rates of primarily used antifungal agents vary considerably in different regions. Therefore, the antifungal therapy for the patients should be decided based on susceptibility tests and previous data on the resistance patterns of possible drugs in that area and not empirical treatment alone to have the most optimal results possible and reduce the rate of antifungal resistance. Furthermore, controlling the infection in healthcare settings plays a significant role in preventing the outbreaks of multidrug-resistant species.

## Conclusion

The study concludes that the incidence of Candidiasis and its antifungal resistance are increasing rapidly in different regions of Iran, and inappropriate drug use can only exacerbate this issue. This analysis emphasizes the increasing resistance, diverse clinical presentations of *Candida* infections, and the need for further research and surveillance. Enhanced diagnostic methods and knowledge of resistance patterns will enable us to face these evolving challenges.

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## Conflict of interest

The authors further declare that they have no conflict of interest.

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