Abstract: The Candida species cause a majority of invasive fungal infections. In this article, we describe the nationwide epidemiology of candidemia in Kuwait in 2018. Yeast bloodstream isolates submitted from all major hospitals and identified by phenotypic MALDI-TOF MS and/or by molecular methods were studied. Susceptibility testing was performed by Etest. Out of 313 bloodstream yeasts, 239 Candida spp. isolates (excluding duplicate isolates) were obtained during 234 candidemic episodes among 223 patients. Mixed-species candidemia and re-infection occurred in 5 and 1% patients, respectively. C. albicans (n = 74), C. parapsilosis (n = 54), C. tropicalis (n = 35), C. auris (n = 33), C. glabrata (n = 32), other Candida spp. (n = 11), and other yeasts (n = 9) caused fungemia. Nearly 50% of patients were in intensive care units. Candida spp. isolates (except C. glabrata) were susceptible to caspofungin and 27% of C. auris were amphotericin B-resistant. Resistance to fluconazole was 100% in C. auris, 17% in C. parapsilosis, 12% in C. glabrata, and 1% in C. albicans. Mortality was 47% for other Candida/yeast infections. Nationwide candidemia incidence in 2018 was 5.29 cases/100,000 inhabitants. Changes in species spectrum, increasing fluconazole resistance in C. parapsilosis, and the emergence of C. auris as a major pathogen in Kuwait are noteworthy findings. The data could be of help in informing decisions regarding planning, in the allocation of resources, and in antimicrobial stewardship.

Keywords: candidemia; Kuwait; incidence; species spectrum; antifungal susceptibility; rare Candida/yeast species; treatment; outcome

1. Introduction

Invasive fungal infections (IFIs) have increased significantly in the last few decades, coinciding with a concomitant increase in the population of immunocompromised/immunosuppressed individuals [1,2]. The spectrum of fungi causing IFIs is changing due to changes in clinical practice [3]. Candida infections constitute a major component of healthcare-associated IFIs and are associated with 20–40% of all-cause mortality, with an attributable mortality of 15–35% in adults and 10–15% in neonates [4–9]. Nearly 50%
of episodes of candidemia occur in intensive care units (ICUs) and contribute towards prolonged hospital stay and considerable health expenditures [10,11].

Previous epidemiological studies have shown that nearly 90% of all Candida infections are caused by only four species/species complexes, which include Candida albicans, Candida tropicalis, Candida parapsilosis, and Candida glabrata [8,12–14]. Among Candida species, C. albicans is considered the most pathogenic and the most frequent cause of candidemia worldwide [15,16]. However, the past two decades have seen a gradual change in the spectrum of species causing candidemia, so much so that >50% of candidemia cases are now caused by non-albicans Candida species, which mainly include C. glabrata complex members, C. parapsilosis complex members, and C. tropicalis as well as many emerging pathogens, likely as a result of the increasing use of fluconazole or other antifungal drugs for prophylaxis or therapy [6,14,17,18]. Candida non-albicans species are associated with even higher rates of mortality and a higher frequency of resistance to antifungal drugs than what is seen with C. albicans infections [6,7,14,19–21]. More recently, the emergence and rapid spreading of the often multidrug-resistant Candida auris has dramatically changed the epidemiology of candidemia at many geographical locations/health care facilities as it has become the most common or one of the more common causes of invasive Candida infections [22].

The annual incidence of candidemia is quite variable in different populations and age groups, with C. albicans causing most infections in younger (<18 years old) patients and C. glabrata infections occurring more frequently among the elderly (>60 years old) [8,17,23–25]. The distribution of candidemia cases caused by major Candida spp. also varies in population-based studies carried out in different countries/geographical settings [6,8,17,23]. Although C. albicans is the most frequently isolated species, the number of candidemia cases caused by C. parapsilosis, C. glabrata, and C. tropicalis vary considerably, while C. auris has recently become a major pathogen in some healthcare facilities/geographical locations [5–8,17,22,23]. C. glabrata is the second, while C. parapsilosis is the third most frequently isolated species from candidemia patients in North America, Australia, and some European countries [5–8,17,23]. The isolation frequency of C. glabrata is particularly higher from patients who are critically ill, have diabetes or exposure to azoles, or have a solid organ transplant or a solid tumor [5,6,8,17,24]. C. parapsilosis is the second most frequently isolated species from candidemia patients in Spain, Latin America, and Africa, and its isolation frequency is higher from patients with indwelling catheters, parenteral nutrition, or prior exposure to antifungal drugs or corticosteroids [6,8,14,17,24]. C. parapsilosis invasive infections are more common in younger individuals, and nearly 34% of all neonatal Candida infections worldwide are caused by C. parapsilosis [6,8,26]. C. tropicalis invasive infections are more common in some Asian settings/countries and patients with these infections are more likely to have hematologic malignancy, neutropenia, or exposure to corticosteroids [6,8,17,24]. C. auris has caused invasive infections and outbreaks in more than 45 countries worldwide and unlike other Candida spp., which predominantly originate from the gastrointestinal tract, it readily colonizes the skin, is shed into the environment, and is easily transmitted to other hospitalized patients [8,22]. C. auris mostly causes invasive infections in older, critically ill patients with indwelling catheters, multiple comorbidities, and prolonged hospitalization [27,28]. Although many epidemiologic studies on invasive Candida infections have been performed, only a few nationwide studies have determined the incidence of candidemia [6,14,29]. This retrospective study determined the countrywide incidence of candidemia in Kuwait in 2018. The study also identified different Candida species that cause bloodstream infections and their resistance to commonly used antifungal drugs.

2. Materials and Methods
2.1. Candidemia Surveillance and Incidence of Candidemia in Kuwait

This retrospective, laboratory-based study performed a nationwide surveillance of candidemia cases in Kuwait from 1 January to 31 December 2018. The study collected data from 8 major and 4 tertiary care hospitals (representing all government hospitals
where candidemia patients are treated in Kuwait) that routinely submit Candida and other yeast bloodstream isolates to the Mycology Reference Laboratory (MRL) for species-specific identification and antifungal drug susceptibility testing. Until the year 2018, all governmental hospitals were distributed over six major medical areas around the country, namely: Capital (central, sea side), Hawally (central, east side), Jahra (north), Ahmadi (south), Farwaniya (central), and the specialized Al-Sabah (central, north side) medical areas. Each major hospital is located in a different medical area, while the tertiary care hospitals are located in the specialized Al-Sabah medical area. The number of hospital beds, catchment area, and various specialties available in these hospitals are shown in Table 1.

Table 1. Number of beds, catchment area, and units/specialties available in different hospitals in Kuwait.

| Hospital Name | Type of Facility | Catchment Area in Kuwait | No. of Beds | Major Units and/or Specialties Available |
|---------------|------------------|--------------------------|-------------|------------------------------------------|
| Adan          | Secondary care   | Ahmadi                   | 826         | MED, SUR, PAE, GAS, PUL, RHE, NEO, CAR, NEU, OBS, and GYN |
| KOC           | Secondary care   | Ahmadi                   | 300         | MED, SUR, PAE, GAS, PUL, RHE, and NEU     |
| MAK           | Secondary care   | Hawally                  | 726         | MED, SUR, PAE, GAS, PUL, RHE, CAR, and NEU |
| Amiri         | Secondary care   | Capital                  | 428         | MED, SUR, GAS, PUL, RHE, CAR, and NEU     |
| Al-Sabah a    | Secondary care   | Central                  | 372         | MED, SUR, PUL, RHE, ENT, and OPT          |
| NBK a         | Tertiary care    | Entire Kuwait             | 67          | P-HAE & P-ONC                            |
| Farwaniya     | Secondary care   | Farwaniya                | 868         | MED, SUR, PAE, GAS, PUL, RHE, NEO, NEU, OBS, and GYN |
| Jahra         | Secondary care   | Jahra                    | 765         | MED, SUR, PAE, GAS, PUL, RHE, NEO, OBS, and GYN |
| Maternity     | Specialized      | Capital, Hawally         | 453         | NEO, OBS, and GYN                        |
| Ibn Sina b    | Tertiary care    | Entire Kuwait             | 355         | Burn, NEU, NES, P-HAE, P-SUR, and KT      |
| KCCC b        | Tertiary care    | Entire Kuwait             | 199         | A-HAE, A-ONC, and BMT                     |
| Chest         | Tertiary care    | Entire Kuwait             | 323         | CAR, Cardiac, Pulmonary and Thoracic specialties |
| Al-Razi       | Tertiary care    | Entire Kuwait             | 465         | Orthopedic                               |

KOC, Kuwait Oil Company; MAK, Mubarak Al-Kabeer; NBK, National Bank of Kuwait; KCCC, Kuwait Cancer Control Center; MED, medical; SUR, surgical; PAE, pediatric; GAS, gastroenterology; PUL, pulmonology; RHE, rheumatology; NEO, neonatology; CAR, careology; NEU, neurology; OBS, obstetrics; GYN, gynecology; ENT, ear, nose, and throat; OPT, ophthalmology; P-HAE, pediatric hematology; P-ONC, pediatric oncology; NES, neurosurgery; P-SUR, pediatric surgery; KT, kidney transplantation; A-HAE, adult hematology; A-ONC, adult oncology; BMT, bone marrow transplantation. a Al-Sabah Hospital shares laboratory services with NBK Hospital. b Ibn Sina Hospital shares laboratory services with KCCC.

Patients’ demographic data and the location of care at the onset of candidemia (or fungemia for other yeasts) were also recorded. The blood samples were obtained from each patient after obtaining verbal consent only as part of routine patient care and diagnostic work-up. For each patient, the first blood culture isolate growing the Candida species during the study period indicated an episode of candidemia. Positive blood cultures yielding the same Candida species within 30 days of the first isolation were attributed to the same candidemia episode and were not included. Recurrent candidemia (re-infection) was defined as a positive blood culture occurring at least one month after the previous episode of candidemia. Mixed candidemia cases indicated the presence of more than one Candida species during the same episode. The data on the total population of Kuwait in 2018 were obtained from the Public Authority for Civil Information (https://www.csb.gov.
2.2. Isolation and Species-Specific Identification of Yeast Isolates

The microbiology laboratories of all government hospitals use automated blood culture systems, including BACTEC 9240 (Becton Dickinson, Sparks, MD, USA), BacT/Alert 3D (bioMérieux, Marcy-l’Etoile, France), and/or Versa TREK™240 (Thermo Fisher Scientific, Waltham, MA, USA) for the isolation of yeasts from blood specimens. All growth-positive blood cultures received in the MRL were subcultured on Sabouraud dextrose agar and Mast ID-CHROMagar Candida (Mast Diagnostics, Merseyside, UK) for phenotypic colony characteristics, as described previously [30]. Species-specific identification was achieved through assimilation profiles obtained by commercial VITEK 2 yeast identification system and/or through protein profiles by MALDI-TOF MS (VITEK® MS) (bioMérieux, Marcy-l’Etoile, France), as described previously [31,32]. A multiplex PCR assay was used to differentiate C. parapsilosis sensu stricto from C. orthopsilosis and C. metapsilosis, as described previously [33]. PCR amplification of rDNA was used to confirm the identification of all C. auris and C. lusitaniae isolates by using species-specific primers, as described previously [30,34]. The identity of selected isolates and other isolates which showed unusual phenotypic characteristics and/or resistance to antifungal drugs was confirmed by PCR sequencing of the internal transcribed spacer (ITS) region of rDNA by using panfungal primers, as described previously [35].

2.3. Antifungal Drug Susceptibility Testing (AST) and the Molecular Basis of Drug Resistance

The in vitro susceptibility to four (fluconazole, voriconazole, amphotericin B, and caspofungin) antifungal drugs was determined by using Etest strips (bioMérieux, Marcy l’Etoile, France) and the data were interpreted according to the manufacturer’s instructions. C. krusei ATCC 6258 and C. parapsilosis ATCC 22019 were used as reference strains for the purpose of quality control. Minimum inhibitory concentration (MIC) values were interpreted as susceptible, intermediate/susceptible dose-dependent, or resistant according to Clinical and Laboratory Standard Institute (CLSI) susceptibility breakpoints (supplement M60) [36]. If an isolate scored as resistant or intermediate to caspofungin, it was also tested against micafungin to confirm the results. Due to the lack of defined breakpoints, isolates showing an MIC \( \leq 1.0 \) µg/mL for amphotericin B were taken as wild-type, and isolates with MIC > 1 µg/mL were scored as non-wild-type [37]. Since there are no established C. auris-specific susceptibility breakpoints, tentative MIC breakpoints of \( \geq 32 \) µg/mL for fluconazole, \( \geq 2 \) µg/mL for voriconazole, \( \geq 4 \) µg/mL for caspofungin, and \( \geq 2 \) µg/mL for amphotericin B (Etest MIC of 1.5 µg/mL was rounded off to 2.0 µg/mL), based on expert opinion, were used [22,38].

The molecular basis of resistance to fluconazole in C. albicans isolates was determined by sequence analysis of the ERG11 gene. The complete ERG11 gene (1578 bp) and the flanking 5′ and 3′ regions were amplified as 5 overlapping fragments and sequenced. The N-terminal fragment, internal fragments 1, 2, and 3, and the C-terminal fragment were amplified and sequenced by using the CalERG11F1 + CalERG11R1, CalERG11F2 + CalERG11R2, CalERG11F3 + CalERG11R3, CalERG11F4 + CalERG11R4, and CalERG11F5 + CalERG11R5 primers (Table 2), respectively, with the reaction and cycling conditions, as described previously [39].

The complete ERG11 sequence was assembled and compared with the reference sequence from the fluconazole-susceptible C. albicans strain SC5314 (GenBank accession no. X13296). The presence of the Y132F mutation in ERG11 in C. parapsilosis or the presence of the Y132F or K143R mutation in ERG11 in C. auris isolates was determined, as described previously [39,40]. The C. glabrata isolate, which showed reduced susceptibility to caspofungin by Etest was analyzed for hotspot-1 (HS-1) mutations in the FKS1 and FKS2 genes [41]. The HS-1 regions of the FKS1 and FKS2 genes were amplified and sequenced, as described previously [41].
Table 2. The DNA sequences of forward and reverse primers and their location in ERG11.

| Primer Name   | Fragment Location | Nucleotide Position | Direction | DNA Sequence |
|---------------|-------------------|---------------------|-----------|--------------|
| CalERG11F1    | N-terminal fragment | −415 to −394        | Forward   | 5′-CACGACAACCTTCAAAAGATTTGA-3′ |
| CalERG11R1    | N-terminal fragment | 149 to 127          | Reverse   | 5′-AATGGAGCTCTATCTTCTTCTAA-3′ |
| CalERG11F2    | Internal fragment 1 | −93 to −71          | Forward   | 5′-AAAGAAGGGAATTCGTTA-3′ |
| CalERG11R2    | Internal fragment 1 | 576 to 554          | Reverse   | 5′-TTGAGTTTTCTCACATTTGGC-3′ |
| CalERG11F3    | Internal fragment 2 | 440 to 462          | Forward   | 5′-AATTTGGCTTTGACTACTG-3′ |
| CalERG11R3    | Internal fragment 2 | 1043 to 1021        | Reverse   | 5′-AAATCACCAACCTTTTCTTCA-3′ |
| CalERG11F4    | Internal fragment 3 | 909 to 931          | Forward   | 5′-TTTCTTTGCTGTACACATA-3′ |
| CalERG11R4    | Internal fragment 3 | 1445 to 1424        | Reverse   | 5′-GTTCCCAATTGACAGCA-3′ |
| CalERG11F5    | C-terminal fragment | 1315 to 1337        | Forward   | 5′-TTTAACCTCTTTGATTGAAGCA-3′ |
| CalERG11R5    | C-terminal fragment | 1762 to 1739        | Reverse   | 5′-ATTAGTCTACCTCAAATTCAC-3′ |

*Nucleotide position is shown relative to the start codon (+1 nucleotide).

2.4. Statistical Analyses

The incidence of candidemia was calculated as the number of candidemia cases per 1,000,000 population. Patients’ demographic data and other variables were compared by the Pearson’s Chi-square test or Fisher’s exact test, as appropriate. Statistical analyses were carried out by using WinPepi software ver. 11.65 (PEPI for Windows, Microsoft Inc., Redmond, WA, USA). A *p value < 0.05 with the use of a two-tailed test was considered statistically significant.

3. Results

3.1. Epidemiology of Candidemia in Kuwait in 2018

A total of 313 bloodstream yeast isolates were submitted to MRL from January to December 2018. Excluding duplicate isolates and non-Candida yeasts, 239 Candida spp. isolates were obtained during 234 candidemic episodes among 223 patients. The demographic details and the hospital unit housing the candidemia patients in 8 major and 4 tertiary care hospitals are shown in Table 3. The number of male patients (n = 122) was slightly higher than females (n = 100) (Table 1). Age distribution was bimodal, mainly involving extremes of age as neonates/infants (<1-year old, n = 51) and senior citizens (≥65 years old, n = 87) were the dominant age groups. The nationality data were available for only 65 patients and included 55 Kuwaiti nationals and 10 non-Kuwaiti patients (2 patients from Saudi Arabia and 1 patient each from United Arab Emirates, Syria, Jordan, Egypt, India, Nepal, Bangladesh, and Sri Lanka). Nearly half (n = 119) of the patients were in the ICU, but their proportion was significantly different among the hospitals (Table 1). All neonates/infants in the Maternity Hospital were in the neonatal ICUs. Excluding the Adan, Jahra, and Farwaniya hospitals, which also have maternity wards and neonatal ICUs, the number of patients located in the ICU was lower in Amiri Hospital or significantly lower (*p < 0.05) in Mubarak Al-Kabeer Hospital compared to the number of candidemia patients in Al-Sabah Hospital or Ibn-Sina Hospital (Table 3). The incidence of candidemia in Kuwait in 2018 was determined as 5.29 cases per 100,000 inhabitants (234 candidemia episodes/4.42 million inhabitants). The incidence was slightly higher in females (6.18/100,000) than in males (4.71/100,000). The highest incidence was detected among infants/neonates (89.1/100,000), followed by the elderly (≥65-year-old group) (62.46/100,000), the 50–64-year-old group (3.81/100,000), and the >1–19-year-old group (1.99/100,000); the lowest incidence (1.69/100,000) was found in the 20–49-year-old group. Nearly 10% of the affected neonates were twins.
Table 3. Distribution of candidemia patients in eight major hospitals and other tertiary care hospitals in Kuwait in 2018.

| Hospital          | Total No. of Patients | Gender | No. Candidemia of Patients of Different Age (years) | Hospital Unit |
|-------------------|-----------------------|--------|---------------------------------------------------|---------------|
|                   |                       | Male   | Female | <1 | ≥1–19 | ≥20–49 | ≥50–64 | ≥65 | ICU | Ward |
| Adan              | 38                    | 24 a   | 13 a   | 10 | 3    | 2     | 13     | 22  | 16  |
| Mubaral Al-Kabeer | 36                    | 17     | 19     | 0  | 5    | 2     | 10     | 9   | 31  |
| Amiri             | 14                    | 5      | 9      | 0  | 0    | 2     | 2      | 10  | 3   |
| Al-Sabah          | 21                    | 16     | 5      | 0  | 3    | 3     | 10     | 9   | 11  |
| Ibn Sina          | 18                    | 9      | 9      | 0 a| 2 a  | 7 a   | 4 a    | 4 a | 10  |
| Maternity         | 33                    | 16     | 17     | 33 | 0    | 0     | 0      | 33  | 0   |
| Jahra             | 15                    | 8      | 7      | 2  | 7    | 1     | 1      | 4   | 8   |
| Farwaniya         | 33                    | 18     | 15     | 3  | 1    | 8     | 6      | 15  | 16  |
| Others *          | 15                    | 9      | 6      | 0  | 1    | 3     | 4      | 7   | 7   |

* Details of one patient were not available. * Other hospitals included Ahmadi Kuwait Oil Company Hospital, Chest Diseases Hospital, Al-Razi Orthopedic Hospital, and Kuwait Cancer Control Center.

The spectrum of Candida spp. isolated during 234 candidemia episodes are shown in Table 4. Candidemia due to two species (C. albicans + C. tropicalis, n = 3; C. albicans + C. parapsilosis, n = 1; and C. glabrata + C. krusei, n = 1) occurred simultaneously in five patients. Eleven patients experienced re-infection at least 30 days after the onset of the first candidemic event; eight patients had re-infection with the same species (C. auris, n = 3; C. parapsilosis, n = 2; C. tropicalis, n = 2; and C. glabrata, n = 1), while three patients had re-infection with a different species (C. krusei followed by C. glabrata, n = 1; C. albicans followed by C. auris, n = 1; and C. glabrata followed by C. auris, n = 1). Among 239 Candida bloodstream isolates, C. albicans was detected in 74 out of 239 (31%) isolates and affected patients of all age groups (Table 4). C. albicans infections occurred either alone (n = 69) or as mixed infection (n = 4) or as initial infection, followed by re-infection with C. auris (n = 1). C. parapsilosis (54 of 239, 22.6%), C. tropicalis (35 of 239, 14.6%), C. auris (33 of 239, 13.8%), and C. glabrata (32 of 239, 13.4%) were the second, third, fourth, and fifth most frequently isolated species, respectively. Other Candida species were isolated from 11 patients, including one patient co-infected with C. krusei and C. glabrata. The isolation frequency of C. albicans from neonates/infants was higher than C. parapsilosis and C. glabrata, and significantly higher (p < 0.05) than C. tropicalis and C. auris. C. parapsilosis (n = 54) was the most dominant non-albicans Candida species; similar to C. albicans and C. tropicalis, it was also isolated from all age groups. More importantly, C. auris was the fourth most common cause of candidemia in Kuwait in 2018, surpassing C. glabrata, and its isolation frequency among older (≥65 years old) patients was significantly higher than C. albicans (p = 0.001).

Table 4. Spectrum of Candida species isolated from candidemia patients in Kuwait in 2018.

| Age (in years) of Candidemia Patients | Candida Species Isolates Identified as |
|--------------------------------------|---------------------------------------|
|                                      | C. albicans, n = 74 | C. parapsilosis, n = 54 | C. tropicalis, n = 35 | C. auris, n = 33 | C. glabrata, n = 32 | Others *, n = 11 |
| <1                                   | 27                      | 13                      | 2                      | 0                      | 0                      | 6                      | 7                        |
| ≥1–19                                | 6                       | 9                       | 2                      | 1                      | 0                      | 0                      | 0                        |
| ≥20–49                               | 11                      | 7                       | 10                     | 7                      | 8                      | 0                      | 0                        |
| ≥50–64                               | 11                      | 2                       | 4                      | 5                      | 4                      | 1                      | 1                        |
| ≥65                                  | 19                      | 23                      | 16                     | 20                     | 14                     | 3                      | 1                        |
| Unknown                              | 0                       | 0                       | 1                      | 0                      | 0                      | 0                      | 0                        |

* C. krusei, n = 4; C. lusitaniae, n = 3; C. blastiki, n = 1; C. dubliniensis, n = 1; C. guilliermondii, n = 1; C. pelliculosa, n = 1.

The isolation frequency of Candida spp. from candidemia patients in all eight major and four tertiary care hospitals was also analyzed with respect to their point of care; the data are presented in Table 5. C. albicans was mostly (48 of 74, 64.9%) isolated from patients in the ICUs and was the dominant species (18 of 37, 48.6%) in Maternity Hospital as well as in...
Adan Hospital (15 of 38, 39.5%), with the latter also including maternity wards and neonatal ICUs catering mainly to the southern governorates within Kuwait. *C. parapsilosis* was the dominant species in only one major (Mubarak Al-Kabeer) hospital, while *C. tropicalis* was most frequently isolated from patients in two major (Amiri and Ibn-Sina) hospitals. More interestingly, in 2018, *C. auris* emerged as the dominant species in two major (Al-Sabah, 14 of 24, 58.3% and Farwaniya, 11 of 36, 27.8%) hospitals in Kuwait, surpassing even *C. albicans* and *C. parapsilosis*. Nine patients had fungemia due to other (*Cyberlindnera fabianii, n = 4; Magnusiomyces capitatus, n = 2; Kodamaea ohmeri, n = 1; Lodderomyces elongisporus, n = 1; and Rhodotorula minuta, n = 1*) yeast species.

### Table 5. Distribution of *Candida* species among candidemia patients admitted into wards and ICUs of eight major and other hospitals in Kuwait.

| Hospital Name | Unit | C. albicans | C. parapsilosis | C. tropicalis | C. auris | C. glabrata | Other Candida Species a | Total |
|---------------|------|--------------|-----------------|---------------|---------|------------|------------------------|-------|
| Adan ICU      | 12   | 2            | 1               | 1             | 6       | 0          | 22                     |       |
| Ward          | 3    | 5            | 3               | 1             | 3       | 1          | 16                     |       |
| Mubarak Al-Kabeer ICU | 2    | 1            | 0               | 0             | 1       | 2          | 6                      |       |
| Ward          | 11   | 13           | 7               | 0             | 4       | 1          | 36                     |       |
| Amiri ICU     | 0    | 0            | 2               | 0             | 0       | 0          | 2                      |       |
| Ward          | 3    | 1            | 5               | 2             | 3       | 0          | 14                     |       |
| Al-Sabah ICU  | 1    | 1            | 1               | 8             | 1       | 0          | 12                     |       |
| Ward          | 1    | 3            | 2               | 6             | 0       | 0          | 12                     |       |
| Ibn-Sina ICU  | 2    | 2            | 3               | 3             | 0       | 0          | 10                     |       |
| Ward          | 0    | 3            | 4               | 1             | 0       | 0          | 8                      |       |
| Maternity ICU | 18   | 8            | 0               | 0             | 4       | 0          | 4                      | 34    |
| Ward          | 0    | 0            | 0               | 0             | 0       | 0          | 0                      |       |
| Jahra ICU     | 2    | 3            | 2               | 0             | 0       | 1          | 1                      | 9     |
| Ward          | 4    | 1            | 1               | 0             | 0       | 0          | 6                      |       |
| Farwaniya ICU | 5    | 2            | 2               | 7             | 1       | 1          | 1                      | 18    |
| Ward          | 4    | 3            | 2               | 4             | 5       | 0          | 18                     |       |
| Others * ICU  | 6    | 5            | 0               | 0             | 2       | 1          | 1                      | 14    |
| Ward          | 0    | 1            | 0               | 0             | 1       | 0          | 2                      |       |
| **Total**     | 74   | 54           | 35              | 33            | 32      | 11         | 239                    |       |

* C. krusei, n = 4; C. lusitaniae, n = 3; C. blankii, n = 1; C. dubliniensis, n = 1; C. guilliermondii, n = 1; C. pelliculosa, n = 1. * Other hospitals included: Ahmadi Kuwait Oil Company Hospital, Chest Diseases Hospital, Al-Razi Orthopedic Hospital, and Kuwait Cancer Control Center.

#### 3.2. AST Data and Molecular Basis of Antifungal Drug Resistance

The AST data against four (amphotericin B, fluconazole, voriconazole, and caspofungin) commonly used antifungal drugs for the five common *Candida* spp. are presented in Table 6. All *C. tropicalis* isolates were susceptible to all four antifungal drugs, while only one *C. albicans* isolate was resistant to fluconazole and voriconazole. Resistance to fluconazole among *C. parapsilosis* was high, as 9 of 54 (16.7%) isolates were resistant to this drug. As expected, many *C. parapsilosis* isolates also exhibited reduced susceptibility to caspofungin, but the MIC values were within the susceptible range. All *C. auris* isolates (*n = 33*) appeared susceptible to caspofungin (MIC range of 0.016–0.5 µg/mL) but were uniformly resistant to fluconazole, while six (18.1%) isolates were additionally resistant to voriconazole. Resistance to amphotericin B was also detected in 9 of 33 (27.3%) isolates. Resistance to fluconazole was also detected in 4 of 32 (12.5%) *C. glabrata* isolates. All four isolates also showed higher MIC (>0.5 µg/mL) to voriconazole and were considered resistant [14]. One *C. glabrata* isolate was intermediate to caspofungin and also showed reduced susceptibility (MIC of 0.095 µg/mL) to micafungin by Etest.
Table 6. Antifungal Susceptibility Data of Candida Species Isolates against Four Antifungal Drugs by Etest.

| Candida Species | Antifungal Drug | MIC Range (µg/mL) | GM ± SD | Resistant, n (%) |
|-----------------|-----------------|-------------------|---------|-----------------|
| C. albicans (n = 74) | Amphotericin B | 0.012–0.19 | 0.05 ± 0.04 | 0 |
|                  | Fluconazole     | 0.047–8         | 0.58 ± 1.14 | 1 (1.4) |
|                  | Caspofungin     | 0.003–0.19      | 0.06 ± 0.056 | 0 |
|                  | Voriconazole    | 0.002–1         | 0.03 ± 0.13 | 1 (1.4) |
| C. parapsilosis (n = 54) | Amphotericin B | 0.002–0.5      | 0.05 ± 0.13 | 0 |
|                  | Fluconazole     | 0.19–256        | 1.43 ± 39.91 | 9 (16.7) |
|                  | Caspofungin     | 0.064–1.5       | 0.32 ± 0.2  | 0 |
|                  | Voriconazole    | 0.002–1         | 0.04 ± 0.21 | 1 (1.9) |
| C. tropicalis (n = 35) | Amphotericin B | 0.002–0.5      | 0.115 ± 0.123 | 0 |
|                  | Fluconazole     | 0.19–1.5        | 0.7 ± 0.36  | 0 |
|                  | Caspofungin     | 0.004–0.25      | 0.08 ± 0.06 | 0 |
|                  | Voriconazole    | 0.012–0.19      | 0.07 ± 0.05 | 0 |
| C. auris (n = 33)  | Amphotericin B | 0.047–2         | 0.855 ± 0.419 | 9 (27.3) |
|                  | Fluconazole     | 32–256          | 212.66 ± 62.13 | 33 (100) |
|                  | Caspofungin     | 0.016–0.5       | 0.24 ± 0.14 | 0 |
|                  | Voriconazole    | 0.047–3         | 0.59 ± 0.89 | 6 (18.1) |
| C. glabrata (n = 32) | Amphotericin B | 0.047–0.75     | 0.19 ± 0.2  | 0 |
|                  | Fluconazole     | 3–256           | 13.91 ± 7.38 | 4 (12.5) |
|                  | Caspofungin     | 0.012–0.38      | 0.11 ± 0.07 | 1 * (3) |
|                  | Voriconazole    | 0.064–16        | 0.28 ± 0.92 | 4 (12.5) |

* Intermediate; MIC, minimum inhibitory concentration; GM, geometric mean; SD, standard deviation.

PCR sequencing data showed that the fluconazole-resistant C. albicans isolate (Kw150/8/18) contained two nonsynonymous mutations (T123I and Y132H) in addition to a few synonymous mutations in ERG11. Fluconazole resistance-conferring mutations (Y132F or K143R) in ERG11 were detected in C. auris isolates. PCR sequencing studies of the HS-1 of the FKS1 and FKS2 genes showed that the C. glabrata isolate (Kw154/7/18), with reduced susceptibility to echinocandins, contained an S663P mutation in the HS-1 of FKS2.

3.3. AST Data of Other Candida/Yeast Species, Clinical Details of Patients, Treatment, and Outcome

The AST data of 11 other Candida spp. and 9 other yeast species isolates are presented in Table 7. All four C. krusei isolates exhibited reduced susceptibility/resistance to fluconazole but were susceptible to voriconazole, amphotericin B, and caspofungin. Three C. lusitaniae and one C. dubliniensis isolates were uniformly susceptible to all four antifungal drugs (Table 7). Similarly, C. blankii, C. guilliermondii, and C. pelliculosa isolates were also susceptible to voriconazole, amphotericin B, and caspofungin but showed reduced susceptibility to fluconazole. Among nine other yeast species isolates, all C. fabianii (n = 4) and L. elongisporus were susceptible to all four antifungal drugs. Both M. capitatus isolates showed resistance to caspofungin, with one isolate also showing reduced susceptibility to fluconazole and amphotericin B. Both K. ohmeri and R. minuta isolates were resistant to fluconazole, with R. minuta showing additional resistance to caspofungin (Table 7).
Table 7. Demographic and clinical details of patients infected with other Candida/yeast species, susceptibility data, treatment given, and outcome.

| Patient No. | Hospital | Unit   | Gender | Age | Date of Onset of Fungemia | Isolate No. | Candida or Yeast spp. | Etest MIC (µg/mL) for | Antifungal Treatment | Outcome              | Reference          |
|-------------|----------|--------|--------|-----|---------------------------|-------------|-----------------------|----------------------|----------------------|---------------------|--------------------|
| 1           | MAK      | Ward   | Female | 77  | 18.01.2018                | Kw217/1/18  | C. krusei            | 0.25, 8, 0.125, 0.25 | CFG, 14 days        | Discharged, 22.07.2018 | This study         |
| 2           | MAK      | ICU    | Female | 58  | 16.04.2018                | Kw183/4/18  | C. krusei **         | 0.75, 48, 0.25, 0.25 | CFG, 6 days         | Expired, 24.04.2018  | This study         |
| 3           | Maternity ICU | Female   | 5 Days  | 07.10.2018 | Kw136/10/18                      | C. krusei     | 0.004, 64, 0.25, 0.094 | L-AMB, 14 days | Not available  | This study         |
| 4           | KOC      | ICU    | Male   | 73  | 19.08.2018                | Kw210/8/18  | C. krusei            | 0.25, 32, 0.19, 0.19 | Not available        | Not available        | This study         |
| 5           | Maternity ICU | Male   | 15 Days | 05.12.2018 | Kw94/12/18                      | C. lusitaniae | 0.016, 0.25, 0.012, 0.032 | L-AMB, 14 days | Discharged, 19.12.2018 | This study         |
| 6           | Farwaniya ICU | Female | 28 Days | 30.12.2018 | Kw39/1/2019                      | C. lusitaniae | 0.016, 0.38, 0.016, 0.008 | L-AMB, 14 days; CFG, 15 days | Discharged, 18.02.2019 | This study         |
| 7           | Jahra    | ICU    | Male   | 9   | 11.08.2018                | Kw51/6/18   | C. lusitaniae        | 0.047, 0.25, 0.006, 0.125 | L-AMB, 21 days        | Discharged, 29.07.2018 | This study         |
| 8           | Maternity ICU | Male   | 4 Months | 14.03.2018 | Kw142/3/18                      | C. blankii   | 0.125, 12, 0.38, 0.25 | L-AMB, 14 days | Discharged, 06.12.2016 | [42]               |
| 9           | Adan     | Ward   | Male   | 5   | 17.05.2018                | Kw205/5/18  | C. guilliermondii    | 0.032, 4, 0.094, 0.38 | Not available        | Not available        | This study         |
| 10          | Maternity ICU | Male   | 3 Days  | 21.05.2018 | Kw251/5/2018                     | C. pelliculosa | 0.023, 6, 0.19, 0.032 | L-AMB, 14 days | Discharged, 06.12.2018 | This study         |
| 11          | MAK      | ICU    | Female | 76  | 14.08.2018                | Kw152/8/18  | C. dublinensis       | 0.016, 0.38, 0.064, 0.01 | CFG, 3 days          | Expired, 26.08.2018  | This study         |
| 12          | Maternity ICU | Male   | 1 Month | 14.03.2018 | Kw80/4/18                       | C. fabianii  | 0.25, 2, 0.125, 0.38 | L-AMB + CFG, 14 days; FLU + CFG, 14 days | Discharged, 28.05.2018 | This study         |
| 13          | Amiri    | ICU    | Male   | 54  | 26.06.2018                | Kw146/7/18  | C. fabianii          | 0.5, 2, 0.064, 0.094 | None *               | Expired, 27.06.2018  | This study         |
| 14          | Maternity ICU | Male   | 8 Days  | 28.07.2018 | Kw303/7/18                      | C. fabianii  | 0.064, 6, 0.19, 0.047 | L-AMB, 14 days | Not available        | This study         |
| 15          | Maternity ICU | Male   | 3 Months | 09.09.2018 | Kw106/9/18                      | C. fabianii  | 0.5, 1.5, 0.094, 0.094 | L-AMB, 6 weeks | Discharged, 27.03.2019 | This study         |
| 16          | MAK      | ICU    | Female | 67  | 20.09.2018                | Kw159/9/18  | M. capitatus         | 1.5, 12, 0.5, 32    | None *               | Expired, 21.09.2018  | [43]               |
| 17          | Amiri    | ICU    | Female | 85  | 03.06.2018                | Kw86/6/18   | M. capitatus         | 0.5, 3, 0.19, 32    | None *               | Expired, 06.06.2018  | [43]               |
| 18          | MAK      | Ward   | Male   | 71  | 21.02.2018                | Kw261/2/18  | L. longisporus       | 0.012, 0.125, 0.004, 0.064 | CFG, One dose only | Expired, 22.02.2018  | This study         |
| 19          | Amiri    | Ward   | Female | 79  | 25.10.2018                | Kw25/11/18  | K. ohmeri            | 0.008, 256, 0.19, 0.19 | None *               | Expired, 27.10.2018  | This study         |
| 20          | Adan     | Ward   | Female | 28  | 29.10.2018                | Kw162/11/18 | R. minuta           | 6, 256, 2, 32        | Not available        | Not available        | This study         |

AMB, amphotericin B; FLU, fluconazole; VOR, voriconazole; CFG, caspofungin; L-AMB, ambisome; n.A., not available. * No treatment was given as the patients expired before culture produced a positive result.

** Mixed infection with C. glabrata.
Fifteen of 20 patients with candidemia caused by other *Candida* /yeast species were admitted into the ICUs and their age varied from 5 days to 85 years (Table 7). The treatment details and outcome were available for 8 of 11 candidemia patients infected with other *Candida* species, and for 7 of 9 fungemia patients infected with other yeast species (Table 7). All three neonates infected with *C. lusitaniae* and one neonate with *C. pelliculosa* were successfully treated with liposomal amphotericin B alone, or with liposomal amphotericin B followed by caspofungin (Table 7). Similarly, one infant with *C. blankii* candidemia was also successfully treated with liposomal amphotericin B (Table 7). Overall, 2 of 8 (25%) patients infected with other *Candida* spp. died, including one patient co-infected with *C. krusei* and *C. glabrata* (Table 7). On the contrary, 5 of 7 (71.4%) fungemia patients due to rare yeast species died, including one patient who had received only a single dose of an antifungal drug and four patients in whom treatment was not even initiated as they succumbed to infection even before the culture produced a positive result (Table 7).

4. Discussion

Candidemia is the most common form of invasive candidiasis; however, it only represents nearly 75% of all invasive *Candida* infections. Furthermore, nearly 30% of all invasive *Candida* infections do not yield a positive blood culture [8,23,45]. Although the impact of candidemia and invasive candidiasis on morbidity, mortality, and healthcare costs is substantial, studies on candidemia on a population-based scale are challenging [6,8–10,14,46–48]. In this study, we determined the nationwide incidence of candidemia, the spectrum of *Candida* species, and their susceptibility to antifungal drugs in Kuwait in 2018. Kuwait is a small country located in the northwest portion of the Arabian Gulf in the Middle East. The country has a largely urban population that lives in the sprawling Kuwait City, with its suburbs divided into several governorates and two smaller towns nearly 45 Km away from Kuwait City; Ahmadi is located in the south and Jahra is located in the west. The total population of nearly 4.4 million individuals in 2018 comprised 1.34 million Kuwaiti nationals and 3.08 million expatriate workers or their dependents, mainly originating from south-southeast Asian, Middle Eastern, and African countries [49,50]. The expatriate workforce in Kuwait in 2018 mostly comprised younger adults. Thus, the contribution of 30–59-year-old expatriate individuals was >68% of their total population, while the corresponding value for Kuwaiti nationals was ~31% (https://www.csb.gov.kw/Pages/Statistics_en?ID=67&ParentCatId=1, accessed on 14 July 2021). There are eight major and four tertiary care government hospitals located within a distance of ~45 Km from Kuwait City [51,52], which are where candidemia patients are diagnosed and treated in Kuwait.

Our nationwide data on the incidence of candidemia in Kuwait in 2018 showed that 234 candidemic episodes occurred in 223 patients. The incidence of candidemia in Kuwait in 2018 was determined as 5.29 cases per 100,000 inhabitants, which is closer to the incidence in Israel and many European countries but lower than that reported from the United States of America (USA) [23,24,29,53,54]. A similar incidence rate has also been estimated for other nearby countries in the Middle East region [47]. Although most European countries have reported an incidence of candidemia between 1.4 and 5.7 cases per 100,000 inhabitants, Spain (8.1 cases per 100,000) and Denmark (>10 cases/100,000) have reported incidence values which are nearly 2–3 times that of the European average [8,23,24,46,55,56]. Similarly, studies from the USA have also reported higher incidence values, with a total of ≥7 cases per 100,000 inhabitants [23,24,54,57]. Epidemiological studies from China (26 cases per 100,000 hospital admissions compared to 90 cases per 100,000 patients in the USA) have also reported incidence values which are comparable to the data from Kuwait and European countries [23,24,58–60]. One study from Thailand, however, reported a higher incidence rate of 13.3 per 100,000 individuals [61]. The highest incidence rate of 89.1 cases per 100,000 was detected among neonates/infants, followed by 62.46 cases per 100,000 for the elderly (≥65 years old) in Kuwait, while the data from the USA showed the highest incidence rate of 20.1 cases per 100,000 among the elderly [54]. Only Spain
has previously reported a higher incidence rate than Kuwait (96.4 cases per 100,000) for invasive candidiasis among children <1-year old [55], while Scotland has reported an incidence rate of 55.9 cases per 100,000 inhabitants among the elderly (≥65 years old), which is comparable to Kuwait [62]. Other European countries and the USA have reported incidence rates among children <1-year old or the elderly that were only 2–5 times higher than the national average [23,24,54]. This large difference between the total incidence rate and the incidence rate among neonates/infants or the elderly is likely due to the large number of 30-year-olds to 59-year-olds, mostly physically fit expatriate workers in Kuwait. This is consistent with the observations that the incidence of candidemia is dependent upon many factors such as the reference (total population, hospital admissions, or ICU admissions) used, the age of the patients (particularly the number of patients at the extremes of age), the overall health of the total population, and the number of patients with malignancies, transplants, or abdominal surgery [8,23].

Species distribution among candidemia patients showed that *C. albicans* was the predominant species but accounted for only 74 of 239 (31%) of all *Candida* spp. isolates, followed by *C. parapsilosis* (54 of 239, 22.6%) and *C. tropicalis* (35 of 239, 14.6%). The data showed that the contribution of *C. albicans* is steadily declining in Kuwait; from a high of 56% during the period of 1994–1998 to 41.8% between 2006 and 2011, and further to 33.1% during the period of 2012–2017 [18]. This decline continued in 2018 as well. A similar trend has also been noted in many other countries where non-albicans *Candida* species now account for the majority of invasive *Candida* infections [8,14,23,24,48,63]. On the contrary, one study from South Korea reported an increasing trend in the incidence of *C. albicans* candidemia in recent years [64]. The second most common *Candida* species isolated from patients with invasive candidiasis varies with geographical locations and is identified as *C. parapsilosis* in Latin/South America and many European and Middle Eastern countries, or as *C. glabrata* in North America, or as *C. tropicalis* in east/southeast Asian countries [8,14,23,24,65]. More recent studies have shown that *C. tropicalis* has now surpassed *C. albicans* as the predominant *Candida* species among candidemia patients in some south-southeast Asian countries [8,66,67]. An important finding of our study was the emergence of *C. auris* as the fourth most common *Candida* species isolated from candidemia patients, replacing *C. glabrata* and its emergence as the predominant species in two major (Al-Sabah and Farwaniya) hospitals in Kuwait. Furthermore, its isolation frequency among older (>65 years old) patients was higher than *C. glabrata* or *C. parapsilosis*, and significantly higher than *C. albicans*. The emergence of *C. auris* as a major bloodstream pathogen has dramatically changed the epidemiology of invasive candidiasis in many countries in recent years [22]. Unlike other *Candida* species, *C. auris* has caused major outbreaks in many healthcare centers around the world [22]. *C. auris* has now emerged as the predominant yeast pathogen in many healthcare centers and geographical locations [68–71].

Consistent with our previous studies [18,32], resistance to antifungal drugs among bloodstream *C. albicans* and *C. tropicalis* isolates was rare as only 1 of 74 *C. albicans* isolates exhibited in vitro resistance to fluconazole and voriconazole only. While the rate of resistance to fluconazole among *C. albicans* isolates in Kuwait is comparable to the worldwide data, fluconazole resistance among global *C. tropicalis* isolates is more common, particularly among isolates from east/southeast Asian countries [8,14,67]. The only triazole-resistant *C. albicans* isolate (Kw150/8/18) detected in this study contained two nonsynonymous (T123I and Y132H) mutations in *ERG11*, which are well-known to confer resistance of *C. albicans* to fluconazole [72]. Resistance of *C. parapsilosis* to fluconazole appears to be increasing consistently in Kuwait as 9 of 54 (16.7%) isolates in 2018 were resistant to this drug. Previously, only 1 of 310 (0.3%) and 21 of 446 (4.7%) *C. parapsilosis* isolates recovered in Kuwait during the periods from 2006 to 2011 and from 2012 to 2017, respectively, were detected as fluconazole-resistant strains [18]. Molecular genetic studies have shown that only ~40% of fluconazole-resistant *C. parapsilosis* isolates in Kuwait contain *ERG11* mutations, while the molecular basis of resistance in the remaining isolates remained unclear [39].
Consistent with previous reports [40,73], fluconazole resistance-conferring mutations (Y132F or K143R) in ERG11 were also detected in the C. auris isolates described in this study. Although 31 C. glabrata isolates were susceptible, one isolate was intermediate to caspofungin. The latter isolate (Kw154/7/18) also exhibited reduced susceptibility to micafungin (MIC of 0.095 µg/mL) by Etest. PCR sequencing studies identified the S663P mutation in the HS-1 of FKS2. Clinical C. glabrata isolates are usually highly susceptible to micafungin (MIC values ≤ 0.03 µg/mL by both Etest and the broth microdilution-bases EUCAST method) [41,74]. This is the first report of the isolation of a bloodstream C. glabrata isolate in Kuwait showing reduced susceptibility to echinocandins and carrying the S663P mutation in the HS-1 of FKS2. Previously, the S663P mutation in the HS-1 of FKS2 was only detected among non-blood (mainly urine) C. glabrata isolates from Kuwait [41]. Although the treatment history and outcome of infection were not available for this patient, our results support previous findings that FKS mutations are a better predictor of non-susceptibility of C. glabrata to echinocandins as compared to Etest [41,75].

Among 11 other Candida spp. isolates, C. lusitaniae isolates were susceptible to all four antifungal drugs tested, while isolates of C. krusei, C. blankii, C. guillermondii, and C. pelliculosa exhibited reduced susceptibility to fluconazole but were susceptible to caspofungin, which is consistent with data reported in other studies [14,18,34,76,77]. Among other yeast species, L. elongisporus and C. fabianii isolates were susceptible to all four antifungal drugs, while R. minuta and M. capitatus isolates showed non-susceptibility to fluconazole and caspofungin. These data are also consistent with recent observations showing that rare Candida/yeast species exhibit non-susceptibility to antifungal drugs, including echinocandins [78–80].

The treatment details and outcome were available for 8 of 11 patients with other Candida and for 7 of 9 patients with rare yeast infections. Although the overall mortality among patients infected with other Candida/yeast species was 47%, higher mortality (71%) was seen among patients infected with rare yeast species. One of 2 patients with C. krusei infection died. This patient was also co-infected with C. glabrata. A higher mortality rate has been observed in candidemia patients infected with C. krusei as compared to those infected with C. albicans, C. tropicalis, or C. parapsilosis [81,82]. All three patients infected with C. lusitaniae were neonates who were successfully treated with liposomal amphotericin B, with/without additional treatment with caspofungin. The findings are similar to data reported for candidemia due to C. lusitaniae among neonates in Kuwait in a previous study [34]. Similarly, the neonate and infant infected with C. pelliculosa and C. blankii [42], respectively, were also successfully treated with liposomal amphotericin B. Amphotericin B has also been previously used successfully for the treatment of C. pelliculosa candidemia patients [83,84], while fluconazole treatment for C. blankii fungemia was not very effective (45% mortality) according to a recent study from India [85]. One of 3 fungemia patients infected with C. fabianii died even before culture results were obtained and treatment could begin, while all four patients infected with other rare yeasts expired, including three patients in whom blood cultures subsequently produced a positive result. A 20% mortality rate was also recently reported in an outbreak among neonates due to C. fabianii in Kuwait [86]. An overall mortality rate of 71% was seen among patients infected with rare yeast species. Our data are consistent with recent reports showing that fungemia due to rare yeast pathogens in both pediatric and adult patients is usually associated with mortality rates higher than those seen with common Candida species, particularly among patients receiving echinocandin therapy [82,87,88].

Our study has a few limitations. The candidemia incidence values described in this study were calculated based on the blood cultures received in the MRL. Since some blood cultures may not have been sent from individual hospitals to MRL, the actual candidemia incidence in Kuwait may be slightly higher. The antifungal susceptibility testing was performed by the Etest and not via the reference broth microdilution method. The clinical details, including the nationality, antifungal treatment given, and the outcome were not available for many patients.
In conclusion, the incidence of candidemia for the whole population of Kuwait was determined and was found to be 5.29 cases per 100,000 inhabitants. However, the incidence of candidemia showed wide variations among different population sections, with the highest incidence reported among neonates/infants, followed by the elderly (≥65 years old) subjects, while the lowest incidence was found among the 20–49-year-old group, largely due to the high number of younger and healthier expatriate workers in the country. Only 74 of 239 (31%) Candida spp. bloodstream isolates were identified as C. albicans, indicating that the vast majority (~70%) of candidemia cases in Kuwait are now caused by non-albicans Candida. Interestingly, C. auris has emerged as the fourth most common cause of candidemia, surpassing C. glabrata, and was also the predominant species in two major hospitals in Kuwait in 2018. Resistance to fluconazole appears to be increasing, particularly among C. parapsilosis isolates in Kuwait; C. glabrata, with reduced susceptibility to echinocandins, was also isolated for the first time from a candidemia patient in Kuwait. Infections with other Candida/other yeast species were also detected and were associated with high (>45%) mortality rates. This study provides an understanding of the epidemiology of invasive fungal infections in Kuwait and calls for the continuous monitoring of incidence and resistance trends as well as the emergence of clinically relevant yeast species, which may have a positive impact on patient care, infection control, and antifungal stewardship.

The DNA sequencing data reported in this study have been submitted to GenBank under accession no. LR137062 to LR137065, LS482924, MZ620708 to MZ620711, and MZ675666 to MZ675675.

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**Data Availability Statement:** All the data are available in the published article; the datasets are available from the corresponding author and can be provided upon reasonable request.

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