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Incidence, Species Distribution, and Antifungal Susceptibility of Candida Bloodstream Infections in a Tertiary Algerian Hospital

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Abstract: Candida infections are the most frequent invasive fungal diseases. To date, few studies have been conducted on candidemia in Algeria. The aim of this study was to assess the incidence, species distribution and antifungal susceptibility for Candida bloodstream infections. This prospective, monocentric study covered all episodes of candidemia diagnosed in the ICU at Setif hospital in Algeria. Yeasts isolates were identified using MALDI TOF. Antifungal susceptibility testing was performed using sensititre yeast one. The incidence rate was 7,03 cases per admission in the ICU. Five Candida species were isolated: *C. albicans*, *C. glabrata*, *C.parapsilosis*, *C.tropicalis* and *C.pelliculosa*. Overall, 78,6 % of isolates were sensitive to all antifungals.

Keywords: Candida spp; candidemia; incidence; Antifungals; resistance

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1. Introduction

Candidemia is the most common invasive fungal infection among hospitalized patients. It is associated with a high rate of morbidity and mortality in hospitalized patients, especially those in intensive care units (ICUs) [1]. While this infection has been extensively studied in America, Europe, and Asia, it remains understudied in Algeria [2-4]. Recognizing variations in incidence, identifying high-risk populations, Understanding species distribution, and assessing antifungal susceptibility patterns are crucial for establishing effective infection control measures and managing this disease. In order to gain a better understanding of this pathology in our region, a one-year prospective study was conducted at Sétif hospital in Algeria. The objective of this study was to determine the incidence, species distribution, and antifungal susceptibility of Candida bloodstream infections.

2. Materials and methods

2.1. Study design

This is a prospective study conducted over a one-year period, from October 2017 to November 2018, in the intensive care units of the University Hospital of Sétif in Algeria. Candidemia was defined as one positive blood culture for Candida species in clinically suspected ICU patients. Demographic characteristics were taken from the medical records.

2.2. Identification and Antifungal Susceptibility

Blood samples were incubated in a BacT/ALERT 480 system (bioMérieux, Marcy-l'Étoile, France). Candida species identification was performed at the time of diagnosis using several methods, including chromogenic agar media (Candida ID2; bioMerieux, Marcy l'Etoile, France), germ tube tests, rice extract agar, and the API ID 32C system (bioMérieux, Marcy l'Etoile, France). All species were further confirmed using MALDI-TOF (Bruker or Biomerieux). Antifungal susceptibility testing for fluconazole, itraconazole, voriconazole, posaconazole, amphotericin B, caspofungin, micafungin, and anidulafungin was performed using the Sensititre YeastOne colorimetric plate (Trek Diagnostic Systems, Cleveland, OH). MIC results were interpreted based on species-specific clinical breakpoints established by the Clinical and Laboratory Standards Institute (CLSI) [5].

2.3. Statistical analysis

The incidence of candidemia was expressed in episodes per 1000 ICU admission. Qualitative variables were expressed in terms of frequency and percentage, and quantitative variables in terms of the mean and standard deviation.

3. Results

During the study period, blood cultures were requested for 102 hospitalized patients, and 14 patients developed at least one episode of candidemia. 13,72% of blood cultures were positive. The cumulative incidence of candidemia in the hospitalized population was 7,03 per 1000 admissions in the intensive care units, with an incidence density was 1,15 cases per 1000 patient-days. The average age of patients with candidemia was 30,82 ± 24,87years (range 44 days–71 years) and 49% were male. The average length of stay in ICU was 15,70 ± 16,06 days (2 to 80 days). Five Candida species were isolated from blood samples. *Candida albicans* was the most predominant, accounting for 42,9% (6 isolates), followed by *C. glabrata* and *C. parapsilosis*, each accounting for 21.4% of the species (3 isolates for each). *C. tropicalis* and *C. pelliculosa* were each detected in only one sample (7,14%). Overall, 78,6 % of isolates were sensitive to all antifungals. One isolate of *C.glabrata* was resistant to posaconazole. Resistance to itraconazol was observed in *C.tropicalis*, *C.glabrata*, and *C.pelliculosa*. The susceptibility of *Candida* species to different antifungal agents was detailed in Table 1.

4. Discussion

The incidence of candidemia found in this study is consistent with reports from india (6,51 cases per 1000 admissions in ICUs) and France (6,9 cases per 1000 admissions in ICUs) [6,7]. Conversely, the incidence is much lower than that reported by a study conducted in thirty-two hospitals in Spain, three in Argentina, and one in France (34,3 cases per 1000 admissions) [8]. Studies conducted in Germany, Turkey, Denmark and Egypt reported rates of 0,29 , 1,76, 0,34, 3,3 cases per 1000 ICU admission respectively[9-12].

According to the results of our study, 57% of the patients with candidemia were male. Invasive candidiasis, specifically candidemia, is less common in women than in men. This male predominance aligns with findings from several candidemia studies [12-14].

In our study, the age of patients varied from 44 days to 71 years, with an average age of 30,82 years. This observation is consistent with the findings of a Moroccan study and another conducted in Latin America, where the average ages of patients were 27 and 26 years, respectively [15, 16]. Similar data have been reported in other studies conducted in Turkey and Iran[17, 18]. However, in many studies on candidemia conducted in North America, Europe, and some Asian countries, the average age falls between 50 and 69 years. In these countries, candidemia is linked not only to an increased number of immunocompromised patients but also to an aging population. Indeed, elderly patients exhibit numerous cumulative risk factors [4, 19-21].

Table 1. In vitro susceptibility profile of Candida bloodstream isolates to nine antifungals.

Species	Antifungal agents	0,008	0,015	0,03	0,06	0,12	0,25	0,5	1	2	4	8	16
C.albicans N=6 **(42,9%)**	Fluconazole												
	Itraconazole		1	2	3	1		1					
	Voriconazole		3				4						
	Posaconazole		5										
	Amphorericin B	3											
	5 Fluorocytosine	1			1	2		1					
	Caspofungin		1	3	2	4	2	1	1				
	Micafungin		6										
	Anidulafungin		3	1	2								
C.glabrata N=3 **(21.4**%)	Fluconazole												
	Itraconazole												
	Voriconazole												
	Posaconazole							2(I)	1®				
	Amphorericin B					1	1	1				1	2
	5 Fluorocytosine				3			1	1(I)	1®			
	Caspofungin				3		1		2				
	Micafungin		3										
	Anidulafungin		3										
C.parapsilosis N=3**(21.4**%)	Fluconazole							3	1				
	Itraconazole												
	Voriconazole				1								
	Posaconazole		1			1							
	Amphorericin B			1	3			3					
	5 Fluorocytosine			2									
	Caspofungin				3			3	1				
	Micafungin								1	2			
	Anidulafungin									2			
Other Species N=2(14,3%)	Fluconazole												
	Itraconazole												
	Voriconazole								1				
	Posaconazole					2			2®				
	Amphorericin B					1						1	
	5 Fluorocytosine				1		1						
	Caspofungin			1		1			2				
	Micafungin		1	2		1							
	Anidulafungin				1								

I: intermediate, R: resistant.

C.albicans was the most frequently identified species, accounting for 42,9% of isolated strains, followed by *C. parapsilosis* and *C. glabrata*. Similar findings have been reported in many studies, with a growing trend of candidemia caused by non-albicans species [22, 23]. However, variations exist within these species prevalence. In the United States and many European countries, *C. glabrata* is the most common non-albicans species, comprising one-third or more of all candidemia isolates, while *C. parapsilosis* is generally the second most prevalent [11, 24-26]. Conversely, Spain, Italy, Croatia, some regions of France, Turkey, and Greece have reported a predominance of *C. parapsilosis* among non-albicans species [17, 21, 27, 28]. In Africa and Latin America, the situation varies, with *C. albicans*, *C. parapsilosis*, and *C. tropicalis* being the predominant species. For example, in Brazil, *C.albicans* is the most common, followed by *C. parapsilosis* and *C. tropicalis* [29]. In Chile, it is

C. parapsilosis followed by *C. glabrata* [22]. South Africa shows differences based on hospital type, with *C. albicans* prevailing in public hospitals and *C. parapsilosis* in private sector hospitals [30]. Algiers's Mustapha hospital found *C. parapsilosis* to be the most isolated species [31]. Egypt reported *C. krusei* as the most frequent species [12]. In Asia, a study in the Asia-Pacific region found *C. albicans* to be the most common, with *C. tropicalis* as the second most prevalent [32]. Similar results were found in Korea [33]. India have *C. tropicalis* as the most prevalent species [6]. According to Jesus Guinea, the reasons behind the global distribution of Candida species remain poorly understood. Various factors, including climate, antifungal use in hospitals, and regional patient microbiota, may influence species presence [27].

All Candida species in our study exhibited low MICs (Minimal Inhibitory Concentrations) to amphotericin B (MIC ≤ 1 μg/ml), reinforcing the reliability of this molecule as an empirical choice. While amphotericin B is no longer recommended as the first-line treatment for candidemia in several countries due to the introduction of new antifungals with a more favorable tolerance profile, it still serves as a therapeutic alternative, especially for isolates resistant to azoles and/or echinocandins. Although acquired resistance to amphotericin B remains rare [2, 34]. The impact of prior prescriptions of this molecule on the MICs levels of Candida spp. has been demonstrated [35].

In our study, all azoles were effective against *C. albicans*. However, certain Candida species exhibited resistances to specific azole antifungals. Notably, there has been an increasing trend in recent years of resistance among Candida species, particularly towards fluconazole, in various countries around the world. Previous studies conducted in Europe, South America, and the United States reported low rates of resistance to fluconazole and itraconazole before 2005 [36], however, data from the latter half of the decade revealed an emergence of resistance among nosocomial isolates, not only to azoles but also to echinocandins [37]. The use of azoles for curative or prophylactic purposes has been linked to the selection of less sensitive or resistant species, such as *C. krusei* and *C.glabrata*, as well as the development of resistance in initially susceptible strains, through mutation and/or activation of efflux pumps [38].

While all our isolates were sensitive to echinocandins, caspofungin has only recently become available in Algeria, and micafungin and anidulafungin are not marketed. Selection pressures on naturally less sensitive strains like *C. parapsilosis* or even de novo acquisition of resistance through gene mutation (FKS) could play a role in the future as the use of echinocandins increases [39, 40]. However, reports from certain parts of the world indicate resistance among nosocomial isolates, especially in *C. glabrata*, to echinocandins[2, 41, 42] . Due to their fungicidal properties against Candida species, including those with reduced susceptibility to azole drugs like C. glabrata and C. krusei, as well as their activity against fungal biofilms, echinocandins are now recommended as first-line treatment

5. Conclusion

In conclusion, *C.albicans* was the most frequently isolated species in candidemia episodes, and most species were susceptible to antifungals. However, these findings warrant confirmation with larger cohorts. Indeed, most studies on candidemia are multicentre and retrospective, as this type of infection is less frequent and typically involves some high-risk services.

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