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Candidemia and antifungal susceptibility in Peruvian hospitals

Candidemia y susceptibilidad a antifúngicos en hospitales peruanos

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SUMMARY

Worldwide, *Candida* bloodstream infections have presented an increase in non-*albicans Candida* species and resistance to antifungal agents. ***Objective:*** To describe the microbiological characteristics of consecutive *Candida* blood culture isolates. ***Methods:*** This study analyzed 73 consecutive *Candida* blood isolates recovered between July 2017 and July 2019 from routine patient care at 15 Peruvian hospitals, assessing susceptibility to four antifungal agents. ***Results:*** The species most frequently detected were *Candida parapsilosis* 39 (53.4%), *Candida albicans* 23 (31.5%), and *Candida tropicalis* 5 (6.8%). ***Conclusions:*** All isolates were susceptible to amphotericin B, fluconazole, voriconazole, and anidulafungin. There is a predominance of non-*albicans Candida* cases in Peru and a high susceptibility to current antifungal drugs.

KEYWORDS: Antifungal agents, Candida, Candidemia, Antifungal Drug Resistance

RESUMEN

A nivel mundial, las infecciones del torrente sanguíneo por *Candida* han mostrado un incremento de especies de *Candida* no *albicans* y de resistencia a los agentes antifúngicos. ***Objetivo:*** Describir las características microbiológicas de aislamientos consecutivos de hemocultivos de *Candida*. ***Material y métodos:*** Se analizaron 73 aislamientos consecutivos de *Candida* en hemocultivos recuperados entre julio de 2017 y julio de 2019 durante la atención clínica rutinaria en 15 hospitales peruanos, evaluando la susceptibilidad a cuatro agentes antifúngicos. ***Resultados:***

Las especies más frecuentemente detectadas fueron *Candida parapsilosis* 39 (53,4%), *Candida albicans* 23 (31,5%) y *Candida tropicalis* 5 (6,8%). ***Conclusiones:*** Todos los aislamientos fueron susceptibles a anfotericina B, fluconazol, voriconazol y anidulafungina. Se observa un predominio de casos por *Candida* no *albicans* en el Perú y una alta susceptibilidad a los antifúngicos actualmente disponibles.

PALABRAS CLAVE: Antifúngicos, Cándida, Candidemia, Farmacorresistencia Fúngica

INTRODUCTION

Candida species are a major cause of fungal infections, with *Candida* bloodstream infection being the most common manifestation of invasive candidiasis in high-income countries. There are an estimated 750,000 cases annually, with a mortality rate of 40-55% [1]. In the United States, Northern Europe, and Australia, *Candida glabrata* (*C. glabrata)* is the second most common species after *Candida albicans* (*C. albicans)* [2]. In Latin America, *C. albicans* is the most common species, followed by *Candida parapsilosis* (*C. parapsilosis)* and *Candida tropicalis (C. tropicalis)*.

Resistance rate to fluconazole among *C. parapsilosis* isolates ranged from 3.4% to 7.5% in the United States and from 0% to 6% in Europe [3], while in Asia it is 10% [4]. In Latin America, the resistance rate to fluconazole was below 3%, but slight increases were observed in *C. albicans*, *C. parapsilosis*, and *C. tropicalis* isolates [3]. Studies in Lima, Peru, in 2014 and 2017 identified 7.8% and 2.5% of isolates exhibiting resistance to amphotericin B, fluconazole, voriconazole, and anidulafungin [5,6]. Data from other regions of Peru are lacking.

The increase in non-*albicans Candida* infections and antifungal resistance presents significant challenges in managing *Candida* bloodstream infections. The study aimed to describe the microbiological characteristics of consecutive blood culture isolates from 15 sentinel hospitals across Peru.

METHODS

This study is part of a multicenter prospective hospital-based surveillance study. As part of the VIRAPERU study [7], microbiological surveillance was conducted for five bacterial species and *Candida* spp. Laboratory collaborators at each sentinel hospital were instructed to store any *Candida* spp. Blood isolated in Tryptic Soy Agar vials for shipment to the Alexander von Humboldt Institute of Tropical Medicine (IMT AvH) for further testing. The Inclusion criteria were *Candida* spp. Blood isolates from patients hospitalized at one of the VIRAPERU sentinel hospitals. Exclusion criteria: isolates from outpatients or emergency-only patients. Sentinel hospitals were selected based on the following criteria: secondary or tertiary care level, availability of a functioning clinical microbiology laboratory that performed regular blood culture testing, and willingness of one physician and one laboratory worker to collaborate with the VIRAPERU study.

Consecutive blood culture isolates were obtained between July 2017 and July 2019 from routine patient care of hospitalized patients suspected of bloodstream infections in 15 sentinel hospitals across 12 regions of Peru. The isolates were identified at IMT AvH using standard methods, including CHROMagar *Candida* medium, germ tube test, cycloheximide assimilation, growth at different temperatures, urea assimilation, morphology in cornmeal agar medium, and growth in hypertonic medium [8,9]. Molecular identification was performed using polymerase chain reaction (PCR) techniques. [10]

The susceptibility of isolates to amphotericin B, fluconazole, voriconazole, and anidulafungin was evaluated using the broth microdilution method according to the Clinical and Laboratory Standards Institute (CLSI) M27-Ed4 guidelines [8]. Clinical breakpoints were interpreted using the CLSI M60 document [11]. When clinical breakpoints were unavailable, epidemiologic cutoff values (ECVs) were applied as per the CLSI M59 document [10]. Using ECVs allows differentiation between wild-type isolates, which represent isolates without acquired resistance mechanisms, and non-wild-type isolates, which indicate no detectable resistance mechanisms or reduced susceptibility for an antimicrobial agent evaluated. Susceptibility was defined as the inhibition of growth at or below the minimum inhibitory concentration (MIC) breakpoint. Susceptible-dose dependent (SDD) was defined as a category for fluconazole in which higher doses are needed to treat infections caused by isolates within this category to achieve clinical success [8,9]. Reference strains *C*

parapsilosis ATCC 22019, and *Candida krusei* (*C. krusei)* ATCC 6258 were used as controls. [8]

Ethical approval was obtained from UPCH IRB (100495, 104408) and the ethics committees of all participating hospitals.

RESULTS

A total of 109 consecutive *Candida* blood isolates were collected from 10 hospitals (three in Lima, two in Trujillo, and one each in Tacna, Arequipa, Madre de Dios, Lambayeque, and Loreto; no isolates were obtained from five hospitals). Seventy-nine corresponded to the first isolation per patient; six could not recover, leaving 73 isolates from 10 hospitals in seven country regions. Most isolates came from hospitals in Lima (69.9%; n = 51), and most were non-*albicans Candida* isolates (68.5%; n = 50). The species most frequently detected were *C. parapsilosis* (53.4%; n = 39), *C. albicans* (31.5%; n = 23), and *C. tropicalis* (6.8%; n = 5).

Susceptibility was determined in 72 isolates. All isolates were susceptible to amphotericin B, anidulafungin, and voriconazole. Susceptibility to fluconazole was 95.8% (69/72), with the remaining three *C. glabrata* isolates classified as susceptible-dose dependent (SDD) (Table 1).

Table 1. Susceptibility to antifungals according to the minimum inhibitory concentration (MIC) of Candida isolates obtained from blood cultures.

Species (Numbers of isolates)	Antifungal	Susceptibility			MIC (µg/ml)								
		S/WT	DDS	R	0,03	0,06	0,125	0,25	0,5	1	2	3	4
Candida albicans (23)	Amphotericin B	23				6	8	3	6				
	Anidulafungin	23			23								
	Fluconazole	23					5	14	2	1	1		
	Voriconazole	23			21	1	1						
Candida parapsilosis (39)	Amphotericin B	39				2	20	9	8				
	Anidulafungin	39			1			2	32	4			
	Fluconazole	39					1	11	24	1	2		
	Voriconazole	39			39								
Candida tropicalis (5)	Amphotericin B	5				3	1	1					
	Anidulafungin	5			5								
	Fluconazole	5						1	2	2			
	Voriconazole	5			3	1	1						
Candida glabrata (3)	Amphotericin B	3						1	1	1			
	Anidulafungin	3			3								
	Fluconazole		3										3
	Voriconazole	3				1	2						
Candida famata (1)	Amphotericin B	ND							1				
	Anidulafungin	ND							1				
	Fluconazole	ND							1				
	Voriconazole	ND			1								
Candida guillermondi (1)	Amphotericin B	1					1						
	Anidulafungin	1							1				
	Fluconazole	1							1				
	Voriconazole	ND			1								

S: susceptible; SDD: susceptible-dose dependent; R: resistant; ND: not defined (It does not have CLSI cut-off points or epidemiological cut-off values); WT: Wild Type

DISCUSSION

This study demonstrates that non-*albicans Candida* is the primary cause of *Candida* bloodstream infection in hospitals in Peru, consistent with previous studies [5,6]. Similar results were observed in studies conducted in Europe, China, and other parts of our continent [12,13,14], except in Colombia, where *C. albicans* is more frequently reported. [15]

In Tan et al. [16] 2016 study on *Candida* bloodstream infections in the Asia-Pacific region, *C. albicans* was the most common species (35.9%), followed by *C. tropicalis* (30.7%) and *C. parapsilosis* (15.7%). Similarly, da Matta et al. [3] reviewed 40 studies from 2007 to 2016 on invasive *Candida* infections in Central and Latin America, and they found *that C. albicans* was the most frequent, followed by *C. parapsilosis* and *C. tropicalis*. The prevalence of *C. albicans* and non-*albicans Candida* species varied significantly between hospitals, with a notable rise in non-*albicans Candida* infections. *C. parapsilosis* has emerged as the most frequent non-*albicans Candida* species and the predominant pathogen of invasive candidiasis in neonates. [17]

All the isolates analyzed in this study were susceptible to the four antifungals evaluated. These results contrast with a study conducted at nine hospitals in Lima between 2009 and 2011 that revealed a 7.8% resistance rate to at least one of the following: amphotericin B, voriconazole, anidulafungin, and fluconazole. Similarly, a subsequent study conducted at three hospitals in Lima between 2013 and 2015 identified that 2.5% of isolates were resistant to fluconazole (including *C. albicans*, *C. parapsilosis*, and a *C. krusei* isolate), 11.4% were SDD for fluconazole and voriconazole, and 1.9% were non-wild-type for posaconazole (MIC>0.06), with a higher prevalence observed in non-*albicans Candida* [5,6]. Our study had a smaller sample size compared to previous reports. Additionally, it included a broader spectrum of secondary and tertiary care hospitals across Peru, and in contrast with previous local studies, it did not include specialized and high-complexity hospitals in Lima. These differences could explain the lower resistance rate found in our study. While different susceptibility testing methods were used in the previous studies (E-test) compared with this study (broth dilution), the overall essential agreement between these two methods has been reported to be over 96% for the most prevalent *Candida* species (*C. albicans*, *C. glabrata*, *C. parapsilosis*, and *C. tropicalis*) [18]. Therefore, it is unlikely that the difference in testing methods explains the difference in resistance rate found in our study.

Our investigation did not identify *C. krusei*, a potential multidrug-resistant yeast, due to its intrinsic resistance to fluconazole and rapid development of resistance to other antifungal drugs [19]. The results of our study are aligned with those of Nucci et al. [20], who evaluated 20 centers in Latin America and found most *Candida* isolates highly susceptible to fluconazole, voriconazole, amphotericin B, and anidulafungin. Nucci et al. [20] reported fluconazole resistance only in *C. krusei* (all resistant by definition; n = 18) and *C. glabrata* (7.1%; n = 3), with the majority of SDD cases being *C. glabrata* (92.9%; n = 39). In their study, all isolates were susceptible to voriconazole and amphotericin B, with limited anidulafungin resistance.

Regarding limitations, although most of the participating hospitals were in several regions of Peru, as an effort to provide a decentralized assessment of *Candida* bloodstream infections, a higher number of isolates were collected from the three hospitals in Lima, likely because these larger hospitals perform more blood cultures compared to regional hospitals. A key limitation in many public hospitals in Peru is the reliance on a single blood culture bottle for the diagnosis of bloodstream infections, as described previously [21]. This practice results in frequent missed opportunities for *Candida* detection and as previously noted, does not meet the standardized performance and quality indicators for blood culture processing, thereby compromising diagnostic sensitivity and potentially explaining the lower recovery of *Candida* isolates in this study. Additionally, the absence of comprehensive clinical data for certain participants is another limitation, as this information could have provided further insights into the factors influencing the outcomes.

This study shows a predominance of non-*albicans Candida* species in bloodstream infections among hospitalized patients in Peru during the 2017-2019 period. Importantly, this is one of the first multicenter studies conducted outside Lima, contributing valuable insights into the epidemiology of *Candida* bloodstream infections across different regions of the country. All strains analyzed were susceptible to the four evaluated antifungal agents: amphotericin B, fluconazole, voriconazole, and anidulafungin.

Our findings show a high susceptibility to fluconazole; however, current Infectious Diseases Society of

America guidelines [22] recommend initiating empirical management of candidemia with an echinocandin. Transition to fluconazole is advised within 5–7 days for clinically stable patients with fluconazole-susceptible isolates and negative follow-up blood cultures. While the predominance of non-*albicans* species and their susceptibility patterns support the use of commonly employed antifungals, these findings underscore the importance of routine species identification and antifungal susceptibility testing to guide timely and appropriate therapy. Active surveillance of *Candida* spp. resistance patterns are recommended to reduce the significant morbidity and mortality observed in hospital settings. Despite the limited sample size, this study contributes to identifying the distribution of *Candida* spp. and their resistance patterns in the country.

Future studies should investigate the demographic and clinical characteristics of patients diagnosed with *Candida* bloodstream infection.

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