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Clinical, Microbiological and Resistance Profile of Candidemia and Invasive Pulmonary Aspergillosis in Immunocompromised Patients and ICU Patients in Seven Colombian Hospitals

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ABSTRACT

Background: Candidemia and invasive pulmonary aspergillosis (IPA) are major fungal infections in immunocompromised patients and patients admitted to the intensive care unit (ICU). Considering the few available data in Colombia, we carried out a nationwide study to determine the clinical, microbiological and resistance profile of patients with candidemia and IPA.

Methods: We conducted a multicenter observational study in seven tertiary healthcare settings from four Colombian cities between March 2015 and September 2016. All adult patients who were immunocompromised or admitted to the ICU with *Candida* bloodstream infection or *Aspergillus* pneumonia were included. For the final diagnosis, in addition to a compatible clinical syndrome, one blood culture was required for candidemia and one bronchoalveolar lavage fluid culture for IPA. Fungal identification using Vitek-2 Compact automated system, and broth microdilution susceptibility testing were performed following the methods and breakpoints recommended by the CLSI.

Results: A total of 155 fungal infections in 150 patients were included; 139 episodes were candidemia and 16 were IPA. The most common fungal species were *C. tropicalis* (48, 31%), *C. albicans* (41, 26.5%), *C. parapsilosis* (24, 15.5%), *C. haemulonii* (14, 9%) and *A. fumigatus* (12, 7.7%). Previous hospitalization was reported in 66/150 patients (44%). The median length of stay was 33 days (range 1-204). All patients had comorbidities, mainly other infectious diseases (71, 47%) and cardiovascular diseases (66, 44%). Empirical antibiotics were administered to 140 patients (93%). Empiric antifungal therapy was given to 56 patients (37%) for between 1 to 36 days; the most common antifungal agent was caspofungin (36/56, 64%), followed by fluconazole (20/56, 36%). Most *Candida* isolates were highly susceptible to caspofungin, fluconazole and other azoles. All *Candida* isolates were susceptible to anidulafungin. For amphotericin B, all *Candida* isolates were susceptible except for one *C. krusei* isolate and the majority of *C. haemulonii* isolates (11/14, 79%).

Conclusions: This study provides valuable information regarding the species distribution and antifungal susceptibility profile of *Candida* bloodstream infections in tertiary healthcare settings in Colombia, which is useful for establishing appropriate infection control measures and guidelines for prophylaxis and empirical antifungal treatment.

BACKGROUND

- Candidemia and invasive pulmonary aspergillosis (IPA) are major fungal infections in immunocompromised patients and patients admitted to the intensive care unit (ICU).(1)
- Few data exist regarding the epidemiology of candidemia and IPA in Colombia although a previous Latin American laboratory-based surveillance study determined an incidence of 1.96 candidemia cases per 1,000 hospital admissions in Colombia.(1)
- The aim of our study was to determine the clinical, microbiological and resistance profile of patients diagnosed with candidemia and IPA in hospital settings in Colombia.

METHODS

- This is a multicenter observational study conducted between March 2015 and September 2016 in seven tertiary healthcare settings from four Colombian cities.
- All adult patients who were immunocompromised or admitted to the ICU and diagnosed with candidemia or IPA were eligible for inclusion in the study. A compatible clinical syndrome and the respective fungal isolate (a *Candida* blood isolate or an *Aspergillus* bronchoalveolar lavage fluid culture) were required for diagnosis of either candidemia or IPA. Different fungal species in the same patient were included.
- All hospitals had automated systems which allowed fungal identification at species level in most cases. However, all isolates were sent to CIDEIM for species confirmation using the Vitek-2 Compact automated system (bioMérieux), and broth microdilution susceptibility testing. The antifungal susceptibility tests were performed following the methods and breakpoints recommended by the Clinical and Laboratory Standards Institute (CLSI).(2) In each hospital, an investigator filled out a case report form once a fungal episode was diagnosed. Information about demographics, comorbidities, hospital stay and antimicrobial treatment was recorded. Enrolled subjects were followed until discharge or death.
- Data analysis was performed in Stata® version 10 (StataCorp LP, College Station, TX, USA) using descriptive statistics.
- The study protocol was approved by the ethics committee of each hospital.

RESULTS

- A total of 155 fungal infections in 150 patients were included in this study; 139 episodes were candidemia and 16 were IPA.
- The median age was 61 years (range 18-95), and 53% were females. Previous hospitalization was reported in 66/150 patients (44%).
- As shown in Table 1, *C. tropicalis* (31%), *C. albicans* (26.5%) and *C. parapsilosis* (15.5%) were the most common fungal species. A great variability in the species distribution was observed between the different hospitals. The institution that collected the most fungal isolates (54/155, 35%) was the only to provide *C. haemulonii* and C. *krusei* isolates. The majority of *Aspergillus* isolates (14/16, 88%) were collected in one healthcare institution.
- All patients had underlying conditions, which were mainly other infectious diseases (71, 47%) and cardiovascular diseases (66, 44%). The majority of patients (134/150, 89%) were hospitalized at the ICU. The median length of hospital stay was 33 days (range 1-204).
- Empirical antibiotics were administered to 140 patients (93%). Empirical antifungal therapy was given to 56 patients (37%) for between 1 to 36 days. Caspofungin was the most frequent antifungal agent (36/56, 64%), followed by fluconazole (20/56, 36%).
- The antifungal susceptibility testing of 136 *Candida* isolates is shown in Table 2. For fluconazole, resistance was observed in few isolates of all *Candida* species; most *C. glabrata* isolates (89%) were non-susceptible to fluconazole. Susceptible dose-dependent pattern to fluconazole was also observed in few isolates of all *Candida* species. All isolates were susceptible to amphotericin B except for one *C. krusei* isolate and the majority of *C. haemulonii* (11/14, 79%). Interestingly, all *Candida* isolates were susceptible to anidulafungin. For caspofungin, all *Candida* isolates were susceptible except for three *C. glabrata* isolates which were intermediate.

Table 2. In vitro antifungal susceptibility of *Candida* isolates (*n* = 136*)

Fungal species (*n*)	Antifungal agent	MIC (µg/ml)			S	SDD or I	R
		Range	MIC_{50}	MIC_{90}	*n* (%)	*n* (%)	*n* (%)
C. tropicalis (48)	Amphotericin B	0.125-1	0.5	1	48 (100%)	NA	0
	Fluconazole	0.06-8	0.5	2	45 (94%)	2 (4%)	1 (2%)
	Voriconazole	0.03-0.5	0.06	0.25	43 (90%)	5 (10%)	0
	Itraconazole	0.03-0.5	0.06	0.25	42 (88%)	6 (12%)	0
	Posaconazole	0.03-0.25	0.06	0.25	ND	ND	ND
	Caspofungin	0.03-0.25	0.06	0.25	48 (100%)	0	0
	Anidulafungin	0.03-0.06	0.03	0.06	48 (100%)	0	0
C. albicans (41)	Amphotericin B	0.25-1	0.5	1	41 (100%)	NA	0
	Fluconazole	0.06-8	0.5	2	39 (95%)	1 (2.4%)	1 (2.4%)
	Voriconazole	0.03-0.5	0.06	0.25	35 (85%)	6 (15%)	0
	Itraconazole	0.03-0.5	0.125	0.5	27 (66%)	14 (34%)	0
	Posaconazole	0.03-1	0.06	0.25	ND	ND	ND
	Caspofungin	0.03-0.25	0.03	0.125	41 (100%)	0	0
	Anidulafungin	0.03-0.125	0.03	0.03	41 (100%)	0	0
C. parapsilosis (24)	Amphotericin B	0.25-1	0.5	1	24 (100%)	NA	0
	Fluconazole	0.06-16	1	8	16 (67%)	4 (17%)	4 (17%)
	Voriconazole	0.03-0.5	0.06	0.125	23 (96%)	1 (4%)	0
	Itraconazole	0.03-0.25	0.06	0.25	21 (88%)	3 (12%)	0
	Posaconazole	0.03-0.5	0.03	0.125	ND	ND	ND
	Caspofungin	0.06-1	0.5	1	24 (100%)	0	0
	Anidulafungin	0.03-0.5	0.125	0.5	24 (100%)	0	0
C. haemulonii (14)**	Amphotericin B	1-≥32	3	16	3 (21%)	NA	11 (79%)
	Fluconazole	0.25-≥32	8	16	ND	ND	ND
	Voriconazole	0.03-0.25	0.09	0.25	ND	ND	ND
	Itraconazole	0.03-0-5	0.19	0.5	ND	ND	ND
	Posaconazole	0.03-0.25	0.125	0.125	ND	ND	ND
	Caspofungin	0.03-0.25	0.125	0.25	ND	ND	ND
	Anidulafungin	0.03-0.25	0.06	0.125	ND	ND	ND
C. glabrata (9)	Amphotericin B	0.25-1	0.5	1	9 (100%)	NA	0
	Fluconazole	2-≥32	4	32	NA	8 (89%)	1 (11%)
	Voriconazole	0.06-0.25	0.06	0.25	ND	ND	ND
	Itraconazole	0.125-0.5	0.25	0.5	1 (11%)	8 (89%)	0
	Posaconazole	0.06-0.5	0.125	0.5	ND	ND	ND
	Caspofungin	0.03-0.25	0.125	0.25	6 (67%)	3 (33%)	0
	Anidulafungin	0.03-0.125	0.06	0.125	9 (100%)	0	0

S, susceptible; SDD, susceptible dose-dependent; I, intermediate; R, resistant; NA, not applicable; ND, not defined.
* Three *Candida* isolates (*C. dubliniensis*, *C. guilliermondii* and *C. krusei*) are not presented in this table.
** In the absence of amphotericin B breakpoints, *C. haemulonii* isolates with MIC ≤1 µg/ml were considered susceptible and those with MIC ≥2 µg/ml were considered resistant.

Table 1. Species distribution of 155 fungal infection episodes (candidemia and invasive pulmonary aspergillosis) in Colombia.

Fungal species	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	Hospital F	Hospital G	Overall *n* (%)
C. tropicalis	19	3	4	7	9	1	5	48 (31%)
C. albicans	12	5	2	3	5	7	7	41 (26.5%)
C. parapsilosis	6	1	1	1	4	2	9	24 (15.5%)
C. haemulonii	14	-	-	-	-	-	-	14 (9%)
A. fumigatus	-	-	-	10	-	2	-	12 (7.7%)
C. glabrata	2	2	-	2	1	-	2	9 (5.8%)
A. flavus	-	-	-	2	-	-	-	2 (1.3%)
C. dubliniensis	-	-	-	-	-	1	-	1 (0.7%)
C. guilliermondii	-	-	-	-	1	-	-	1 (0.7%)
C. krusei	1	-	-	-	-	-	-	1 (0.7%)
A. nidulans	-	-	-	1	-	-	-	1 (0.7%)
A. niger	-	-	-	1	-	-	-	1 (0.7%)
Total	54	11	7	27	20	13	23	155

CONCLUSIONS

- This study provides valuable information regarding the species distribution and antifungal susceptibility profile of *Candida* bloodstream infections in tertiary healthcare settings in Colombia, which is useful for establishing appropriate guidelines for prophylaxis and empirical antifungal treatment.
- As reported in other studies, non-*albicans Candida* species accounted for the majority of episodes, but interestingly we found that *C. tropicalis* was by itself the most frequent species in our study.
- Overall, resistance rates to the antifungal agents tested were low. Most *Candida* isolates were susceptible to caspofungin, fluconazole and other azoles. For amphotericin B, all *Candida* isolates were susceptible except for one *C. krusei* isolate and the majority of *C. haemulonii* isolates. All *Candida* isolates were susceptible to anidulafungin.
- A limitation of this study is that although seven reference healthcare settings from different Colombian cities were included, results may not be representative for the entire country.

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