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Clinical and epidemiological characteristics and risk factors for mortality in patients with candidemia in hospitals from Bogotá, Colombia

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ABSTRACT

Background: Bloodstream infection by *Candida* species has a high mortality in Latin American countries. The aim of this study was to describe the characteristics of patients with documented bloodstream infections caused by *Candida* species in third level hospitals and determine the risk factors for in-hospital-mortality.

Methods: Patients from seven tertiary-care hospitals in Bogotá, Colombia, with isolation of a *Candida* species from a blood culture were followed prospectively from March 2008 to March 2009. Epidemiologic information, risk factors, and mortality were prospectively collected. Isolates were sent to a reference center, and fluconazole susceptibility was tested by agar-based E-test. The results of susceptibility were compared by using 2008 and 2012 breakpoints. A multivariate analysis was used to determinate risk factors for mortality.

Results: We identified 131 patients, with a median age of 41.2 years. Isolates were most frequently found in the intensive care unit (ICU). *Candida albicans* was the most prevalent species (66.4% of the isolates), followed by *C. parapsilosis* (14%). Fluconazole resistance was found in 3.2% and 17.6% of the isolates according to the 2008 and 2012 breakpoints, respectively. Fluconazole was used as empirical antifungal therapy in 68.8% of the cases, and amphotericin B in 22%. Hospital crude mortality rate was 35.9%. Mortality was associated with age and the presence of shock at the time of *Candida* detection. Fluconazole therapy was a protective factor for mortality.

Conclusions: Candidemia is associated with a high mortality rate. Age and shock increase mortality, while the use of fluconazole was shown to be a protective factor. A higher resistance rate with new breakpoints was noted.

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Introduction

Candidemia is the main invasive fungal infection that occurs in hospitalized patients; *Candida* species account for almost 80% of fungal pathogens causing nosocomial infections.[1] The incidence of candidemia has increased more than five-fold in the last decade.[2] Recent data show an overall incidence of candidemia ranging from 0.2 to 0.5 cases per 1000 admissions.[3] An incidence ranging from 0.28 to 0.96 cases per 1000 admissions has been found in the United States; in Europe, an incidence of 0.2–0.38 cases per 1000 admissions is estimated.[4] Recently, an incidence of 1.18 cases per 1000 admissions was found in Latin America; in particular, the highest incidence was found in Colombia, with 1.96 cases per 1000 admissions,[5] much higher than the reported incidences in the northern hemisphere, with a trend to increase over the last decade.

Candidemia is associated with prolonged hospital stay, increased costs, and a higher mortality rate that can vary from 25% to 60%.[6] In Latin America, particularly in Colombia, there is little information on epidemiological and clinical aspects of patients with candidemia. The present study describes the clinical and epidemiological characteristics of patients with candidemia in Colombian tertiary-care hospitals. The distribution of species, their fluconazole susceptibility profile, mortality rates, and a multivariate statistical analysis of factors associated with mortality are presented.

Materials and methods

Study design

This was an observational, multicenter study conducted over a period of 12 months on patients who had experienced at least one episode of candidemia between March 8, 2008 and March 7, 2009 in seven tertiary-care hospitals of Bogotá, Colombia. Hospitals that participated in the study after having approved the research protocol were: Instituto Nacional de Cancerología (INC), Hospital Universitario San Ignacio (HUSI), Hospital de San José (HSJ), Fundación CardioInfantil (FCI), Hospital Universitario Clínica San Rafael (HUCSR), Hospital Militar Central (HMC), and Hospital Universitario de la Samaritana (HUS). All of them were high complexity institutions, with intensive care units (ICU, approximately 165 beds), internal medicine and surgery wards. One of them was a reference center for cancer (INC), and four of them had an oncology/hematology ward (INC, HUSI, HSJ, HMC). Three of them were public (INC, HMC, HUS).

Procedures

The study included all patients of any age group admitted to participating institutions during the study period with a diagnosis of infection with yeast of the genus *Candida* in blood, confirmed by microbiology. The clinical laboratories of the institutions included in the study identified and typified the presence of *Candida* in blood cultures using automated methods (BACTEC, Becton Dickinson, USA). The isolates of *Candida* species were referred to the Instituto Nacional de Cancerología, where the strains were typed again in the mycology laboratory (Yeast ID, MicroScan, Dade Behring, Siemens, USA) and their susceptibility to fluconazole was tested by the agar based E-test method. At the same time, epidemiological and clinical information of the patients were prospectively collected, and the patients were followed until discharge or death.

Study variables and definitions

Epidemiological variables, inpatient services, and inpatient days were included. The clinical variables and risk factors were the presence of various comorbidities (tumors, diabetes, chronic renal insufficiency, *etc.*), systemic inflammatory response syndrome (SIRS), organ dysfunction, or shock at diagnosis of candidemia. The main recorded microbiological variable was blood culture positivity time from sampling to the report from the blood culture team. We also recorded several treatment variables. An episode of candidemia was defined as the isolation of a *Candida* species from one or more blood cultures. The age ranges were defined as neonates: $\leq$28 days old or staying in the Neonatal Intensive Care Unit (for the premature); children: age over 28 days up to 18 years; adults: between 19 and 60 years; elderly: $\geq$60 years. For the number of organs involved, the Score Organic Failure (SOFA) scale was used. Abdominal surgery was defined as a recent surgical procedure that involved the gastrointestinal tract within the last two weeks. Prolonged corticotherapy was defined as doses >0.5 mg/kg/day of prednisone or equivalent corticosteroid or cumulative dose higher than 700 mg. Previous fluconazole exposure was any hospital use of fluconazole seven days before the blood cultures were taken in which the *Candidia* species was isolated. The interpretation of susceptibility to fluconazole was initially performed with breakpoints from the Clinical Laboratory Standards Institute (CLSI), 2008 (CLSI 2008) where a minimum inhibitory concentration (MIC) $\leq$8 mg/L is considered susceptible (S), $\geq$64 mg/L resistant (R), and intermediate values susceptible dose-dependent (SDD). *A posteriori* analysis taking into account the existing cutoffs proposed by Pfaller et al. in 2012[7] was conducted. For *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, S was defined as a MIC $\leq$ 2 mg/L, R a MIC $\geq$ 8 mg/L, and SSD intermediate MIC values. For *C. glabrata*, MIC $\leq$ 32 mg/L was considered SDD, and MIC $\geq$ 64 mg/L were considered R. Inappropriate use of fluconazole was defined as the use of fluconazole in patients with resistance to fluconazole by susceptibility testing. Mortality was assessed at 14 days after detection of candidemia and hospital mortality.

Statistical analysis

For descriptive analyses mean and standard deviation (SD) for continuous variables and percentages for categorical data were calculated. For evaluating association between mortality and demographic and clinical variables, preliminary univariate analyses were performed calculating crude odds ratios (ORs). A multivariate analysis of all factors found to be significant on univariate analysis and of the most clinically relevant variables was performed to estimate adjusted ORs. Statistical analyses were performed with Stata 11. All reported *p*-values