Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain

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Abstract

A prospective, multicentre, population-based surveillance programme for *Candida* bloodstream infections was implemented in five metropolitan areas of Spain to determine its incidence and the prevalence of antifungal resistance, and to identify predictors of death. Between May 2010 and April 2011, *Candida* isolates were centralized to a reference laboratory for species identification by DNA sequencing and for susceptibility testing by EUCAST reference procedure. Prognostic factors associated with early (0–7 days) and late (8–30 days) death were analysed using logistic regression modelling. We detected 773 episodes: annual incidence of 8.1 cases/100 000 inhabitants, 0.89/1000 admissions and 1.36/10 000 patient-days. Highest incidence was found in infants younger than 1 year (96.4/100 000 inhabitants). *Candida albicans* was the predominant species (45.4%), followed by *Candida parapsilosis* (24.9%), *Candida glabrata* (13.4%) and *Candida tropicalis* (7.7%). Overall, 79% of *Candida* isolates were susceptible to fluconazole. Cumulative mortality at 7 and 30 days after the first episode of candidaemia was 12.8% and 30.6%, respectively. Multivariate analysis showed that therapeutic measures within the first 48 h may improve early mortality: antifungal treatment (OR 0.51, 95% CI 0.27–0.95) and central venous catheter removal (OR 0.43, 95% CI 0.21–0.87). Predictors of late death included host factors (e.g. patients' comorbid status and signs of organ dysfunction), primary source (OR 1.63, 95% CI 1.03–2.61), and severe sepsis or septic shock (OR 1.77, 95% CI 1.05–3.00). In Spain, the proportion of *Candida* isolates non-susceptible to fluconazole is higher than in previous reports. Early mortality may be improved with strict adherence to guidelines.

Keywords: Antifungal resistance, *Candida* bloodstream infections, early mortality, epidemiology, prognostic factors, surveillance
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Introduction

European surveillance studies show that the incidence of *Candida* bloodstream infections (BSI) ranges from nearly 3 to 8.6 per 100 000 population per year [1–6].

Despite the introduction of new antifungal agents, this infection remains a severe disease associated with significant mortality [7]. Hence, changes in clinical practices have already occurred, with prophylactic and empirical antifungal therapies in high-risk patients. However, these strategies may be linked to a shift towards non-*albicans* species and the emergence of isolates with decreased fluconazole susceptibility [8].

The epidemiology of candidaemia has been extensively studied in the USA [9–12] and northern and central Europe. In Spain, however, data are limited to surveys conducted in specific areas [6,13] or tertiary centres [14]. Furthermore, we are lacking information about the reasons for the poor current outcome of candidaemia. Studies that have reported determinants of mortality are based on retrospective data or have focused on the impact of therapeutic measures from a restricted viewpoint [15–20].

We conducted a population-based surveillance for *Candida* BSI in Spain to determine its incidence and the distribution and susceptibility pattern of *Candida* species, and to examine prognostic risk factors for mortality.

Materials and Methods

Setting, patients and study design

The CANDIPOP study is a prospective, population-based surveillance programme on *Candida* BSI, conducted from May 2010 to April 2011 in 29 hospitals located in five of the largest municipal areas of Spain: Barcelona, Bilbao, Madrid, Seville and Valencia (population 9 498 980, or 20% of the Spanish population). Patients were identified by local laboratories and reported to study coordinators, who collected data using a standardized case report form. Demographic characteristics, underlying conditions, predisposing risk factors within the preceding month, and 30-day follow-up outcome were recorded in a dedicated database created for the study. Given the observational nature of this research, patients were managed according to routine clinical care.

Audits were carried out to ensure that all cases were reported. The study was approved by the local institutional review boards, and written consent was obtained from patients.

Definitions

Definitions have been described in a previous publication [6]. In brief, an incident case was the first positive *Candida* spp. blood culture. Candidaemias occurring >30 days after the incident episode or isolation of a different *Candida* species after the initial case were considered new episodes. Outpatient-acquired cases were candidaemias detected ≤2 days after hospitalization. The Charlson index was used to represent comorbidity in adults [21]. Sepsis, severe sepsis or septic shock were recorded on the day of candidaemia [22]. Proven catheter-related candidaemia has been described elsewhere [23]. Timing to central venous catheter (CVC) removal and to antifungal administration was the interval between incident blood culture and implementation of these measures. Adequate antifungal treatment was the use of the correct dose of antifungal agent for a susceptible *Candida* isolate (see Supplementary material, Table S1). Patients receiving >3 days of systemic antifungal drug before the first positive blood culture were considered to have breakthrough candidaemias.

Incidence

Population and age-specific incidence rates were expressed as number of cases per 100 000 population, using the 2011 Spanish national census data. Overall incidence of hospitals was calculated using as denominators the summed number of admissions and patient-days of each hospital during the study period.

Microbiological studies

Candida isolates were forwarded to a reference laboratory, the Spanish National Centre for Microbiology in Madrid, for species confirmation and antifungal susceptibility testing. Species identification was performed by sequencing the internal transcribed spacer (ITS) regions from ribosomal DNA. ITS1 and ITS2 regions were directly amplified by PCR from yeast suspensions and sequenced using universal primers [24,25]. Susceptibility to antifungal drugs and interpretation of resistance rates were investigated according to the protocols [26,27] and clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [http://www.eucast.org/clinical_breakpoints/]. Of note, *Candida glabrata* and *Candida guilliermondii* are considered intermediate or resistant to fluconazole, as there is insufficient evidence on whether the wild-type population of these pathogens can be considered fluconazole-susceptible.

Data analysis

Quantitative variables are reported as median and interquartile range (IQR) and qualitative variables as number (%). Categorical data were analysed using the chi-squared or Fisher exact test. Significance was set at a p-value of <0.05. Prognostic factors associated with early (0–7 days) and late (8–30 days) death were assessed using logistic regression analysis. To preserve the assumption of independence of observations, only the first episode of candidaemia recorded for an individual patient was included in this analysis. Neonates and infants younger than 1 year were excluded from the