ORIGINAL ARTICLE MYCOLOGY

Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain

M. Puig-Asensio[1,2], I. Ruiz-Camps[1,2], M. Fernández-Ruiz[3], J. M. Aguado[3], P. Muñoz[4,5,6,7], M. Valerio[4,5,6,7], A. Delgado-Iribarren[8], P. Merino[9], E. Bereciartua[10], J. Fortún[11], M. Cuenca-Estrella[12] and B. Almirante[1,2] on behalf of the CANDIPOP Project, GEIH-GEMICOMED (SEIMC), and REIPI

1) *Department of Infectious Diseases, Hospital Universitari Vall d'Hebron,* 2) *Department of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain,* 3) *Infectious Diseases Unit, Hospital Universitario 12 de Octubre, Instituto de Investigación Hospital 12 de Octubre (i+12),* 4) *Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón,* 5) *Department of Medicine, Universidad Complutense de Madrid,* 6) *Instituto de Investigación Sanitaria del Hospital Gregorio Marañón, Madrid, Spain,* 7) *CIBER de Enfermedades Respiratorias (CIBER RES CD6/06/0058), Palma de Mallorca,* 8) *Microbiology Department, Hospital Universitario Fundación de Alcorcón, Alcorcón,* 9) *Clinical Microbiology Department, Hospital Universitario Clinico San Carlos, Madrid,* 10) *Department of Infectious Diseases, Hospital de Cruces, Bilbao,* 11) *Infectious Diseases Department, Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigaciones Sanitarias, IRYCIS,* 12) *Department of Mycology, Spanish National Centre for Microbiology, Instituto de Salud Carlos III, Madrid, Spain*

Abstract

A prospective, population-based surveillance on candidaemia was implemented in five metropolitan areas of Spain from May 2010 to April 2011. We aimed to describe the distribution and susceptibility pattern of *Candida* species, and to evaluate risk factors for mortality in patients with oncological (solid tumours) and haematological malignancies. Adults (≥16 years) with cancer were included in the present report. Impact of therapeutic strategies on 7- and 30-day mortality were analysed by logistic regression, adjusting for propensity score by inverse weighting probability of receiving early antifungal treatment and catheter removal. We included 238 (32.6%) patients (195 oncological, 43 haematological). Compared with oncological patients, haematological patients were more likely to have received chemotherapy (53.5% versus 17.4%, $p < 0.001$) or corticosteroids (41.9% versus 21%, $p < 0.001$), and have neutropenia (44.2% versus 1.5%, $p < 0.001$). Overall, 14.8% of patients developed breakthrough candidaemia. Non-*albicans Candida* species (71.1% versus 55.6%, p 0.056) and *Candida tropicalis* (22.2% versus 7.6%, p 0.011) were more frequent in haematological patients. Based on EUCAST breakpoints, 27.6% of *Candida* isolates were non-susceptible to fluconazole. Resistance to echinocandins was negligible. Mortality at 7 and 30 days was 12.2% and 31.5%, respectively, and did not differ significantly between the patient groups. Prompt antifungal therapy together with catheter removal (≤48 hours) was associated with lower mortality at 7 days (adjusted OR 0.05; 95% CI 0.01–0.42) and 30 days (adjusted OR 0.27; 95% CI 0.16–0.46). In conclusion, non-*albicans* species are emerging as the predominant isolates, particularly in haematological patients. Prompt, adequate antifungal treatment plus catheter removal may lead to a reduction in mortality.

Keywords: Antifungal agents, cancer, Candidiasis, drug resistance, epidemiology, fluconazole, haematological malignancies
Original Submission: 20 August 2014; **Revised Submission:** 11 November 2014; **Accepted:** 30 December 2014
Editor: E. Roilides
Article published online: XXX

This study was partially presented at the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (Poster M-312), San Francisco, CA, USA; 9–12 September 2012

Corresponding author: I. Ruiz-Camps, Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Pg Vall d'Hebron 119-129, 08035 Barcelona, Spain
E-mail: iruiz@vhebron.net
Members of the CANDIPOP Project are listed at the end of paper

http://dx.doi.org/10.1016/j.cmi.2014.12.027

Introduction

Candidaemia is a severe fungal infection closely associated with cancer and the complications of its treatment. Estimates of the incidence of this infection vary substantially because surveillance programmes in this population are scarce and most reports are focused on haematological malignancies [1,2]. Despite improvements in the management of patients with this condition and the introduction of echinocandins, candidaemia 30-day mortality rates range from 35% to nearly 50% [2–5]. In addition, a shift towards an increasing prevalence of non-*albicans* species with potentially decreased fluconazole susceptibility has been reported [6,7]. Unfortunately, there is less related information in patients with solid tumours, but it appears that the species isolated in oncological patients are similar to those in the general population [4,8].

In this study, we present episodes of candidaemia occurring in cancer patients by analysing data from a prospective population-based surveillance in Spain (CANDIPOP study). We aim to describe *Candida* species distribution and antifungal drug resistance in patients with underlying malignancies, to update the prognosis of *Candida* bloodstream infections (BSI) in the oncological and haematological population, and particularly, to assess the impact of therapeutic strategies on mortality.

Material and methods

Study design, setting and patients

The CANDIPOP study was a prospective, population-based surveillance for *Candida* BSI conducted from May 2010 to April 2011 in 29 hospitals located in five metropolitan areas of Spain. The study methods were described previously [9]. Briefly, case reporting was laboratory-based. Each candidaemia episode was reported to regional study collaborators who collected the clinical data and recorded the 30-day follow-up outcome (i.e. survival or death). Patient management and antifungal prophylaxis policy was at the discretion of the attending physician. *Candida* isolates were sent to the Mycology Reference Laboratory at the National Centre for Microbiology in Madrid, Spain, for species confirmation and antifungal susceptibility testing. Species were identified by sequencing the internal transcribed spacer regions 1 and 2 from ribosomal DNA. Susceptibility to antifungal drugs was assessed according to the protocols [10,11] and clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Clinical breakpoints-fungi, Table v 6.1. Available at: http://www.eucast.org/clinical_breakpoints/, accessed 1 May 2013). The study protocol was approved by the ethics committees of the participating centres.

This report focuses on *Candida* BSI episodes in adult patients (≥16 years) with underlying solid organ tumours or haematological malignancies. Patients who had not received treatment for oncological/haematological disease within the previous 12 months were excluded. Only the first episode of candidaemia per patient was included. All patients provided written informed consent for participation.

Definitions

The definitions have been reported elsewhere [9,12]. In summary, proven catheter-related candidaemia was defined as follows: 1) evidence of catheter exit site exudate with the same *Candida* spp. that was isolated from the bloodstream; 2) semi-quantitative culture of the catheter tip yielded >15 CFU of the same *Candida* spp.; or 3) simultaneously quantitative cultures of blood samples showed a ratio of 3:1 of CFU between blood samples obtained through the catheter and a peripheral vein, or the differential time to positivity was ≥2 hours for non-*glabrata* *Candida* BSI [13,14]. Secondary foci required identification of the same *Candida* species at the affected site. Episodes with no defined secondary source or without proven catheter-related origin were classified as primary. Breakthrough candidaemia was established on detection of *Candida* BSI in patients who had been receiving antifungal drugs for >3 days. Neutropenia was described as granulocyte count <500 cell/mm^3 at time of first positive *Candida* species blood culture collection. Severity of illness was measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score for patients admitted to the Intensive Care Unit (ICU) and the Pitt bacteraemia score on the day of candidaemia [15,16]. Adequate antifungal treatment was defined as use of the correct dose of antifungal agent for a susceptible *Candida* isolate. Appropriate fluconazole dosing was 6 mg/kg/day (adjusted for renal function if necessary) except for non-susceptible *Candida* spp., *Candida glabrata*, *Candida guilliermondii* and *Candida krusei*, which was considered inappropriate (see Supporting information, Table S1). Early central venous catheter (CVC) removal was established when the line was removed within 48 hours of the incident BSI, and in patients with multiple CVCs, when at least the responsible CVC was removed within this timeframe.

Statistical analysis

Categorical data are expressed as the count and percentage, and numerical data as the median and interquartile range. Categorical variables were compared with the chi-squared or Fisher exact test, and continuous variables with the Mann–Whitney *U*-test. All statistical tests were two-tailed, and significance was set at $p < 0.05$.

Logistic regression analysis was applied to identify predictive factors of 7-day and 30-day mortality. As our aim was to

Please cite this article in press as: Puig-Asensio M, et al., Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain, Clinical Microbiology and Infection (2015), http://dx.doi.org/10.1016/j.cmi.2014.12.027