Journal of Hospital Infection 87 (2014) 54–58

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Short report

Nosocomial *Candida parapsilosis* candidaemia: risk factors, antifungal susceptibility and outcome

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ARTICLE INFO

Article history:
Received 24 October 2013
Accepted 10 February 2014
Available online 12 March 2014

Keywords:
Candida parapsilosis
Candidaemia
Minimum inhibitory concentration
Minimum fungicidal concentration
Cardiovascular prosthetic materials

SUMMARY

A retrospective analysis was undertaken from 2000 to 2010 to show the risk factors associated with death within 30 days in patients with *C. parapsilosis* candidaemia (CPC). Fifty-one cases of nosocomial CPC were included in the analysis. All isolates from blood cultures were susceptible to micafungin and fluconazole. The overall mortality rate was 23.5%, and the most severe complications were endocarditis (5.9%) and endophthalmitis (5.9%). On multi-variate analysis, APACHE II score >25 (odds ratio 43.9) and retained cardiovascular prosthetic materials (RCPM) (prosthetic valve or graft) (odds ratio 14.6) were found to be risk factors associated with death. Prompt surgical removal should be considered in CPC patients with RCPM.

Introduction

Candida spp. remain a major cause of morbidity and mortality in healthcare settings. *Candida parapsilosis* is often the second or third most commonly isolated *Candida* spp. from blood cultures.[1] Intravenous catheters and parenteral nutrition are well-known risk factors. *C. parapsilosis* demonstrates an increased in-vitro minimum inhibitory concentration (MIC) to echinocandins such as caspofungin.[1] Recent studies have shown increasing incidence of *C. parapsilosis* candidaemia (CPC) of 7–24%.[2]

Although risk factors associated with death attributed to candidaemia have been documented in the literature, any specific risk factors associated with nosocomial CPC are not known. The primary outcome of this study was to establish the risk factors associated with death within 30 days by multivariate analysis. The secondary outcome was to determine antifungal MICs and minimum fungicidal concentrations (MFCs) for *C. parapsilosis* isolated from blood cultures.

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0195-6701/$ – see front matter
http://dx.doi.org/10.1016/j.jhin.2014.02.006

Patients and methods

Study design

A retrospective observational study was performed between 1 April 2000 and 31 March 2010. The setting was Tokyo Women's Medical University (TWMU) Hospital in Japan, a 1423-bedded university hospital that includes the nation's largest institute of cardiovascular disease. All cases of nosocomial CPC were included in the study. The study protocol was approved by the Ethics Committee at TWMU Hospital.

Definitions

A case of candidaemia was defined as a patient with at least one positive blood culture yielding any *Candida* spp. Cases with positive blood cultures occurring 48 h after admission were defined as nosocomial candidaemia. Blood samples were drawn under sterile conditions and processed using BACTEC 9240 (Becton Dickinson Diagnostic Instrument Systems, Towson, MD, USA). *C. parapsilosis* was identified using the API 32C system (bioMérieux, Marcy l'Etoile, France).

Study population

Patients were observed from the day of diagnosis of CPC until the end of follow-up at 30 days. The following data were obtained for all patients: age; sex; underlying disease; use of intravenous catheters; retained cardiovascular prosthetic materials (RCPM) (prosthetic valve or graft); empirical or definitive antifungal treatment; dose of antifungal agents; complications of candidaemia; Acute Physiology and Chronic Health Evaluation (APACHE) II scores at diagnosis of candidaemia; and crude mortality at 30 days. Hepato-biliary-pancreatic cancer was defined as including hepatocellular carcinoma, pancreatic cancer or bile duct cancer. Blood tests including white blood cell and neutrophil counts, serum C-reactive protein and 1,3-beta-D-glucan (BDG) assay using Fungitec G-test MK (Nissui, Tokyo, Japan; cut-off level 20 pg/mL) were performed within three days of a positive blood culture.

Exclusion criteria were: age <16 years; post-haematopoietic stem cell transplantation; end-stage cancer in palliative therapy; human immunodeficiency virus positive; antifungal treatment not initiated; and *Candida* spp. not stored at −80 °C.

Antifungal susceptibility

Until 2012, micafungin was the only approved echinocandin, and caspofungin was not available during the study period in Japan. The MIC values of micafungin, amphotericin-B, fluconazole, voriconazole and itraconazole against *C. parapsilosis* isolated from blood culture were measured retrospectively in accordance with the standards of the Clinical and Laboratory Standards Institute (CLSI) M27-A3 using an Eiken DP kit (Eiken, Tokyo, Japan). The MFC was defined as the lowest drug concentration that resulted in less than one colony.

Statistical analysis

Continuous data were compared using Student's *t*-test, and categorical data were compared using Fisher's exact test. Spearman's rank correlation coefficient was used to show correlation between antifungal MIC and MFC values. $P < 0.05$ and $r > 0.5$ were considered significant. Multi-variate analysis was used to determine the independent risk factors associated with mortality using forward stepwise logistic regression. All variables with $P < 0.1$ on univariate analysis were entered into the multi-variate model. Statistical analyses were performed using R Version 2.14.1 (http://www.r-project.org/) for Microsoft Windows 7.

Results

Clinical features

In total, 307 cases of nosocomial candidaemia were identified. The incidence of nosocomial candidaemia was 0.074 cases per 1000 patient-admission-days during the study period. *C. parapsilosis* ($N = 89$, 29%) was the second most common *Candida* spp. causing candidaemia after *Candida albicans* (43%). Fifty-one of the 89 cases of CPC with medical records met the inclusion criteria and were included in this study.

The demographic and clinical characteristics of the 51 cases (39 survivors and 12 deaths) of CPC are shown in Table I. Eighteen of these 51 (35.3%) patients had digestive tract or hepato-biliary-pancreatic cancer. Seven cases had RCPM, consisting of prosthetic valves ($N = 5$) and grafts ($N = 2$). No significant differences were found between the survivors and the patients who died in terms of receipt of empirical or definitive antifungal treatment, serum C-reactive protein, BDG and white blood cell count. The crude 30-day mortality rate was 23.5% (12/51). APACHE II score >25 [odds ratio (OR) 43.9, 95% confidence interval (CI) 4.77–404; $P = 0.000839$] and RCPM (OR 14.6, 95% CI 1.05–203; $P = 0.0459$) were risk factors associated with death within 30 days on multi-variate analysis (Table I).

The most severe complications identified in this study were endophthalmitis ($N = 3$, 5.9%) and endocarditis ($N = 3$, 5.9%). Two cases developed endophthalmitis during micafungin treatment and one case developed endophthalmitis during fluconazole treatment. Likewise, two cases developed endocarditis during micafungin treatment and one case developed endocarditis during fluconazole treatment.

Analysis of antifungal susceptibility

Antifungal MIC and MFC values and Spearman's rank correlation coefficients between MIC and MFC values are shown in Table II. No reduced susceptibility to antifungal agents (micafungin, fluconazole, itraconazole, voriconazole or amphotericin-B) or resistant strains was found according to breakpoints determined by CLSI and EUCAST. Rank correlations between antifungal MIC and MFC values against *C. parapsilosis* were observed for amphotericin-B ($r = 0.6789$, $P < 0.0001$) and micafungin ($r = 0.5449$, $P < 0.0001$) by Spearman's rank correlation coefficient. In contrast, no correlation between MIC and MFC values was observed for fluconazole ($r = 0.2702$, $P = 0.0504$).

Discussion

To the best of the authors' knowledge, this is the first paper in the English language to report the risk factors associated