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Original article

Distribution of *Candida* species isolated from blood cultures in hospitals in Osaka, Japan

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ABSTRACT

Background: Candida species are clinically important causes of bloodstream infections because their mortality is very high. Given that some species of Candida are azole-resistant, identifying the distributions of Candida species could facilitate the formulation of an appropriate empirical antifungal therapy. It has been shown that the distribution varies depending on the continent, country, city, and hospital. In this paper, we describe the distributions of species in hospitals in northern Osaka, Japan.

Method: We evaluated blood culture results obtained from six tertiary hospitals in the northern Osaka area between 2004 and 2011. We also obtained comorbidity information from the patients' hospital medical records. Kaplan–Meier curves were drawn to compare the risk of death related to the different species.

Results: Of the 165 cases of candidemia confirmed by blood culture, 66% were male and the mean age was 62 years (range = 0–96). Overall, *Candida albicans* comprised 70 cases (43%), followed by *Candida parapsilosis* with 36 cases (22%), *Candida glabrata* with 25 cases (15%), *Candida tropicalis* with 11 cases (7%), *Candida krusei* with 10 cases (6%), and other Candida species with 13 cases (8%). *C. tropicalis* had higher associated mortality than other species, although it was not statistically significant.

Conclusions: C. albicans was the most frequently isolated species, but the proportion of non-albicans Candida species was not negligible. The relatively high frequency of non-albicans Candida species distinguished the Japanese distribution from other areas. This characteristic distribution may have important implications when formulating an empirical antifungal therapy for Japanese clinical practice.

1. Introduction

Candida species are among the most common causes of nosocomial bloodstream infection (BSI) [1]. They are important in clinical settings because the mortality rate associated with candidemia is very high [2,3]. However, conducting an epidemiological study of candidemia is challenging because cultures rarely confirm the infection. Many hospitals in Japan lack suitable facilities for performing reliable mycological assays of *Candida* species. Thus, Japanese physicians use empirical therapy because it is not possible to delay treatment until positive blood culture results are obtained [4]. The incubation time has a statistically significant impact on the in-hospital mortality [5] and delaying empirical treatment for more than 12 h is associated with higher mortality [6].

Numerous surveillance programs have focused on candidemia, which have documented the prevalence of different *Candida* species. In the early 1990s, a population-based surveillance study organized by the Centers for Disease Control and Prevention (CDC) found that *Candida albicans* was the dominant *Candida* species [7], followed by *Candida parapsilosis*. Subsequent surveillance programs have noted an increase in the proportion of non-*albicans Candida* BSI, particularly an increase in *Candida glabrata* [8]. This change in distribution is considered to be important because fungal drug susceptibility testing is not the universal standard of care, so knowledge of the infecting species is used to guide therapy. Both *C. glabrata* and *Candida krusei* are considered to be azole-resistant species [9,10] so any change in the distribution of *Candida* species affects the choice of empirical antifungal therapy. The distribution of *Candida* species varies geographically. In Canada and Europe, for example, the prevalence of *C. albicans* is higher than that in other

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regions. The United States (US) has a higher proportion of *C. glabrata* than other regions, while *Candida tropicalis* is disproportionately prevalent in Latin America [11].

In this study, we determined the distributions of *Candida* species in northern Osaka, Japan using data collected during 2004–2011 from tertiary care hospitals.

2. Methods

2.1. Study design

The data used in this study were obtained from tertiary care hospitals in the northern Osaka area of Japan. Blood culture results were evaluated between 2004 and 2011. Six hospitals in the northern Osaka area participated in this study, including one university hospital (1000 beds), one national center for cardiovascular/cerebral diseases (600 beds), and four city hospitals (360–600 beds for each). We received approvals by the ethical review board in Osaka University Hospitals. This study is registered in UMIN (UMIN000008282). A candidemia case was defined as the first isolation of any *Candida* species from blood drawn from a patient at any of the participating hospitals. Medical records were also reviewed to identify the underlying medical conditions, treatments, and potential risk factors.

The detection and species determination of isolates were performed in each hospital laboratory using CHROMagar (Kanto Chemical Co. Inc., Tokyo, Japan), API 20C AUX (SYSMEX bioMérieux Co. Ltd, Kobe, Japan), or a Vitek Yeast Biochemical Card (SYSMEX bioMérieux Co. Ltd, Kobe, Japan). All of the clinical decisions were entrusted to the discretion of the patient's physician. One hospital lacked suitable technology to determine the species type from 2004 to 2009, so only data obtained from this hospital between 2010 and 2011 were included in the analysis.

When identifying underlying conditions and risk factors, we defined "broad-spectrum antibiotics" as fourth generation cephalosporins and carbapenems. Exposure to broad-spectrum antibiotics, anti-MRSA drugs, and prophylactic antifungal agents were defined as the use of these drugs during the 60 days prior to the blood cultures being taken. A central venous line was counted when it was placed in a patient within seven days before the blood culture was taken. Diabetes mellitus, including impaired glucose tolerance, was a clinical diagnosis made by the reviewers of the medical records in each hospital. Hemodialysis was either chronic hemodialysis or other types of active blood purification therapy within the 60 days prior to the blood test.

2.2. Statistical analysis

The relative frequencies were calculated to compare the distributions of different *Candida* species. Kaplan–Meier curves were also drawn to visualize the survival distributions. SAS version 9.3 (SAS Institute Inc., Cary, NC, US) was used for the statistical analyses.

3. Results

A total of 165 cases were detected. Among them, 81 were detected in the university hospital, 3 were in the national center for cardiovascular/cerebral diseases, and 81 were in city hospitals. Table 1 shows the clinical and demographic characteristics of the patients with candidemia. The mean age was 62 years (range = 0–96) and 66% of the patients were male. One person was found to possess two species types. We treated this patient as two cases in the analysis. The department where *Candida* species were isolated most frequently from blood samples was internal medicine with 62 cases. Internal medicine is an aggregate of all types of internal medicine departments, other than cardiology and hematology/oncology. Gastrointestinal surgery was second with 35 cases. In terms of comorbidities, 129 patients (78%) had central venous line placements within seven days prior to their blood samples being tested, 88 patients (53%) were exposed to broad-spectrum antibiotics before *Candida* isolation, and 125 patients (75%) had been hospitalized for more than 18 days at the time of detection.

Table 1
Characteristics of patients with candidemia ($n = 165$).

Patient characteristics	
Sex (male), *n* (%)	109 (66)
Age (years), mean (SD)	62 (23)
Department, *n* (%)	
Internal medicine	62 (38)
Cardiology	9 (5)
Hematology/oncology	20 (12)
Pediatrics/pediatric surgery	13 (8)
Cardiothoracic surgery	13 (8)
Gastrointestinal surgery	35 (21)
Other surgery	13 (8)
Comorbidity/risk factor, *n* (%)	
Diabetes mellitus	55 (33)
Hemodialysis	22 (13)
Chemotherapy	32 (19)
Immunosuppression	60 (36)
Central venous line	129 (78)
Anti-MRSA drug	20 (12)
Broad-spectrum antibiotics	88 (53)
Fluconazole	19 (12)
Micafungin	44 (27)
Hospital days to isolation, median (25th, 75th percentile)	35 (18, 73)

During the study period, 165 cases of candidemia were confirmed by blood cultures at the participating hospitals. Overall, 42.4% (70 cases) of the infections were due to *C. albicans*, followed by *C. parapsilosis* (21.8%, 36 cases), *C. glabrata* (15.2%, 25 cases), *C. tropicalis* (6.7%, 11 cases), *C. krusei* (6.1%, 10 cases), and other *Candida* spp. (7.9%, 13 cases) (Fig. 1).

The evaluation of the clinical outcomes showed that the 28-day all-cause mortality was 32% for all cases. *C. tropicalis* had a higher in-hospital mortality than other species, although the difference was not statistically significant (Fig. 2). Of the patients who died, 90% died within 31 days of candidemia being diagnosed. With respect to the differences in mortality, the status of comorbidities, rather than the virulence of each species, may explain the higher likelihood of mortality in patients with *C. tropicalis*. In this study, a chi-squared test showed that there was a statistically significant

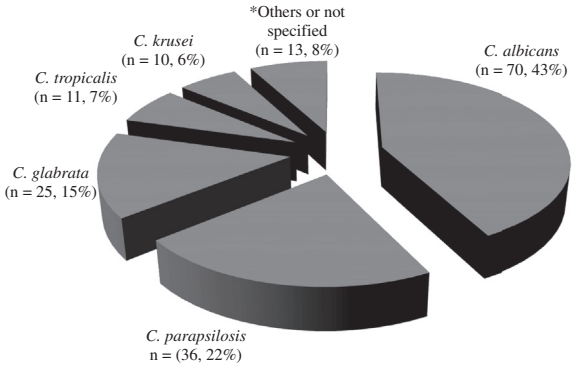

Fig. 1. Overall distribution of *Candida* species ($n = 165$). * One case of *Candida famata*, one case of *Candida lusitaniae*, and 11 cases of undetermined *Candida* species. *C. albicans* is the most frequently isolated, and *C. parapsilosis* follows.