Distribution of candidemia in Malaysian tertiary care hospital revealed predominance of *Candida parapsilosis*

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Abstract. *Candida parapsilosis* is an important pathogen of healthcare-associated bloodstream infections (BSI) causing high mortality and morbidity in immunocompromised patients in addition to other *Candida* species including *C. albicans*, *C. tropicalis*, *C. glabrata*, and *C. krusei*. Knowledge on recent local species distribution and trend is essential. An increase in the proportion of *C. parapsilosis* candidemia has been recently observed as a result of many risk factors. The distribution of candidemia has been changing in the last three decades. To determine the proportion of different *Candida* species causing candidemia in a tertiary-care hospital during January 2001 – December 2018, a retrospective study performed in a 853-bedded tertiary-care hospital in north-eastern Malaysia. All cases of candidemia from January-2001 to December-2018 were included, and the review was performed based on patients' medical records and laboratory database. The frequency of different *Candida* species was determined. This study showed that out of 1175 patients with candidemia, *C. parapsilosis* was the most common species contributing to 29.2% (343/1175) of candidemia, followed by *C. albicans* 20.1% (236/1175), *C. tropicalis* 18.7% (220/1175), *C. glabrata* 6.0% (71/1175), *C. guilliermondii* 3.7% (43/1175), *C. rugosa* 1.9% (22/1175), *C. famata* 1.7% (20/1175), *C. krusei* 1.4% (16/1175), *C. dubliniensis* 0.8% (9/1175), *C. lusitaniae* 0.7% (8/1175), *C. lipolytica* 0.3% (4/1175), *C. pelliculosa* 0.3% (4/1175), *C. haemulonii*, *C. kefyr*, *C. utilis* and *C. inconspicua* (1/1175 each). In addition, 14.9% (175/1175) belonged to *Candida* spp. which were not identified to species level. In conclusion, a different scenario for the proportion of *Candida* species with *C. parapsilosis* predominates over *C. albicans* as a nosocomial pathogen leading to candidemia has been shown in this study.

INTRODUCTION

The incidence of invasive *Candida* infections continues to rise worldwide, especially *Candida* bloodstream infections, due to many factors including increased use of immunosuppressive therapy and invasive devices (Giri & Kindo, 2012; Mohamed *et al.*, 2018).

In the USA, *Candida* has been reported as the fourth most common pathogen causing healthcare-associated bloodstream infections (BSIs) contributing 8-10% of the

cases (Chi *et al.*, 2011; Giri & Kindo, 2012; Yapar, 2014; Amalina, 2018) and ranked sixth in Europe (Caggiano *et al.*, 2015). Bloodstream infections due to *Candida* cause significant mortality and morbidity worldwide (Giri & Kindo, 2012; Santhanam *et al.*, 2013; Mohamed *et al.*, 2018), especially in intensive care units (ICUs) and among immunocompromised patients (Noor, 2008; Tan *et al.*, 2016). Knowledge of recent local trends, species distribution and antifungal resistance is essential for prevention and control strategies (Mohamed *et al.*, 2018).

Currently, *Candida* has been known to have more than 200 known species. However only a small proportion are of medical importance and have been isolated in human infections. These include *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida guilliermondii*, *Candida lusitaniae* and *Candida dubliniensis*. Of these species, 95% of the infections involved *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* (Giri & Kindo, 2012; Yapar, 2014*)*. Recently a multidrug resistant species, *Candida auris*, has emerged as a health-care associated pathogen associated with mortality in hospitalized patients (Chowdhary *et al.*, 2017).

Although *C. albicans* remains the major cause of invasive candidiasis in some regions, infections caused by non-*albicans* species have been recently observed with increasing trends worldwide, including Malaysia (Chi *et al.*, 2011; Santhanam *et al.*, 2013; Amalina, 2018; Mohamed *et al.*, 2018). Among non-*albicans* species, *C. parapsilosis* was reported as one of the major pathogenic *Candida* in Latin America, Canada, Europe and Asia Pacific (Liu *et al.*, 2018)

In particular, the incidence of infections by antifungal resistant non-*albicans Candida* has been increasing during the last several years. An important shift in the type of *Candida* infections, from *C. albicans*, towards a more treatment-resistant non-*albicans Candida* varieties has been observed. Therefore, epidemiological monitoring of pathogenic *Candida* is unquestionably important. Thus, the knowledge of local epidemiological trend of invasive candidiasis, mainly BSIs is an important guidance in therapeutic management (Noor, 2008; Chi *et al.*, 2011; Kazak *et al.*, 2014; Tan *et al.*, 2016; Amalina, 2018).

Herein we report distribution of *Candida* species as causative agent for BSI at a tertiary hospital in Malaysia throughout 2001 and 2018.

MATERIALS AND METHODS

Study Design
This is a cross-sectional retrospective study conducted to analyze episodes of candidemia among patients at Hospital Universiti Sains Malaysia (USM), Malaysia from 1st January 2001 to 31st December 2018. Hospital USM is a 853-bedded tertiary government hospital, with intensive care units and oncology wards. This study was approved by the Human Research Ethics of Universiti Sains Malaysia [USM/JEPeM/16040162].

Clinical and Laboratory Data
Data regarding *Candida* isolation from blood samples and patients' clinical information were obtained from the Hospital USM Laboratory Information System and Medical Records Unit.

Definitions
Candidemia was defined as at least one positive blood culture for *Candida* species in patients with symptoms or signs of infection, whether it was isolated from peripheral or central line.

Candida spp. refers to non-*albicans Candida* species that were not identified to species level.

Case Selection
Inclusion criteria: All in-patients with candidemia from January-2001 to December-2018 were included. Candidemia that occurred more than 30 days after the initial episode were considered as a new episode. Candidemia episodes in same patient but by different species were considered as separate episodes.

Exclusion criteria: Repetitive blood cultures obtained from the same patient with the same *Candida* species within one month were excluded.

Candida Isolation and Identification

The isolation of *Candida* has been performed routinely using standard mycology methods. Commercially available identification systems, namely API 20C AUX® or ID 32C® biochemical identification kit (BioMérieux, Marcy l'Etoile, France) or VITEK® system (BioMérieux, Marcy l'Etoile, France) (last two years) have been used for identification of *Candida* to species level. For API 20C AUX® and ID 32C®, identification percentage threshold of more than 88% was considered as acceptable. Molecular identification using ribosomal RNA gene sequencing was also performed to confirm some isolates with difficult phenotypic identification.

Statistical Analysis

Data was analyzed using SPSS software for windows (Version 24.0; SPSS, Chicago, IL, USA). Descriptive statistical analysis was done. The distribution of different *Candida* species was expressed as proportion and relative frequency.

RESULTS

Species Distribution

A total of 1175 non-repetitive cases of candidemia were identified from January 2001 to December 2018 (Table 1). *C. parapsilosis* was the most commonly isolated species contributing to 29.2% (343/1175) of candidemia, followed by *C. albicans* 20.1% (236/1175). Our data shows that three quarters of all candidemia were due to the four main *Candida* species, *C. parapsilosis*, *C. albicans*, *C. tropicalis*, and *C. glabrata*, and their proportions were 29.2%, 20.1%, 18.7% and 6.0% respectively. Other isolated *Candida* species include *C. guilliermondii* 3.7% (43/1175), *C. rugosa* 1.9% (22/1175), *C. famata* 1.7% (20/1175), *C. krusei* 1.4% (16/1175), *C. dubliniensis* 0.8% (9/1175), *C. lusitaniae* 0.7% (8/1175), *C. lipolytica* 0.3% (4/1175), *C. pelliculosa* 0.3% (4/1175). The rarer ones, *C. haemulonii*, *C. kefyr*, *C. utilis* and *C. inconspicua* contributed one isolate each (1/1175).

The trend of the three most common *Candida* species has been changing over the period of the study (Figure 1). In 2001 the relative frequency of *C. albicans* was the highest, followed by *C. parapsilosis* which then predominated over other *Candida* species, and reached its peak in 2006, in which it accounted for 38% of all candidemia. In 2012 candidemia cases were almost equally distributed between the three *Candida* species. In the last six years *C. parapsilosis* continued to outnumber both *C. albicans* and *C. tropicalis* except in 2018, where *C. tropicalis* outnumbered *C. parapsilosis* and consequently *C. albicans*, accounting to 47% of all candidemia.

A total of 622 *C. parapsilosis* blood isolates have been isolated from patients admitted to different wards from 2001 to 2018 (Figure 2). Out of 622 *C. parapsilosis*

Table 1. Distribution of *Candida* species at HUSM from January 2001 to December 2018

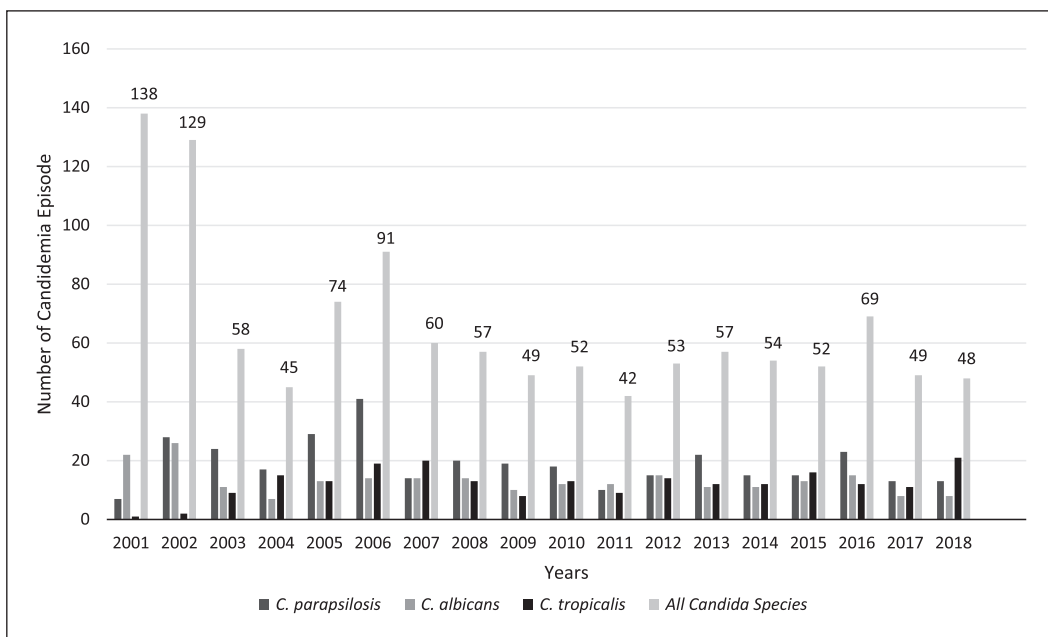| Organism	Number of patients	Percentage %
Candida parapsilosis	343	29.2
Candida albicans	236	20.1
Candida tropicalis	220	18.7
Candida spp.	175	14.9
Candida glabrata	71	6.0
Candida guilliermondii	43	3.7
Candida rugosa	22	1.9
Candida famata	20	1.7
Candida krusei	16	1.4
Candida dubliniensis	9	0.8
Candida lusitaniae	8	0.7
Others	12	1.0

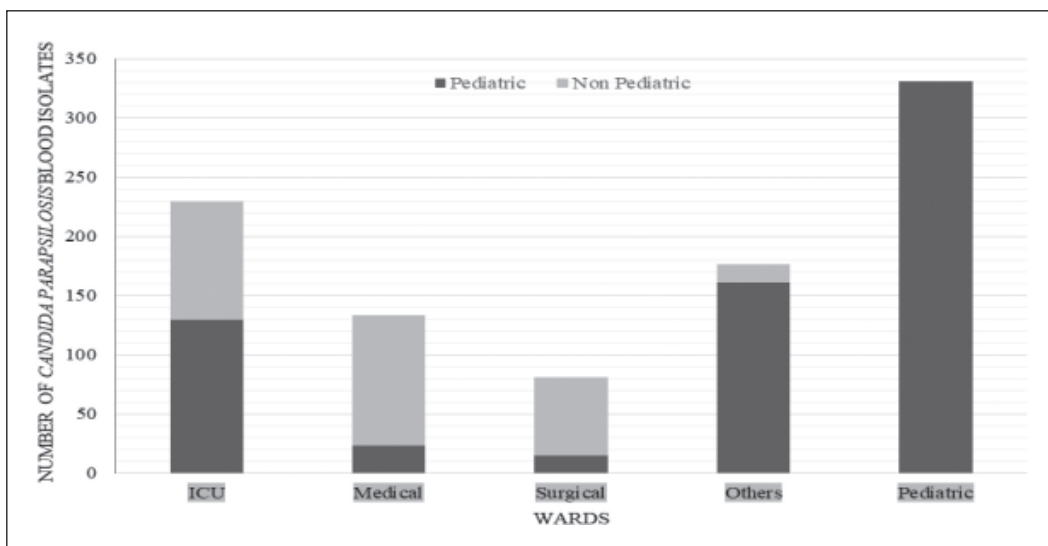Figure 1. Trends of main *Candida* species from 2001 to 2018.

Figure 2. Distribution of *C. parapsilosis* in different wards (2001-2018).

positive blood cultures, 229 (36.8%) isolates were isolated from ICU patients, 133 (21.4%) from medical wards, 81 (13.0%) from surgical wards, and 179 (28.8%) from other locations. Collectively, 331 out of the 622 *C. parapsilosis* isolates were from pediatric wards.

DISCUSSION

Candida species are the most common cause of invasive yeast infections. At least 16 recognized species of *Candida* cause human diseases, while more than 90% of infections are caused by the five most

common pathogens, *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis*, and *C. krusei* (Mohamed *et al.*, 2018). Many factors contribute to the occurrence of candidiasis, including advances in medicine, expansion of human life span and immuno-deficiencies. Advances in medicine such as transplantation of organs and tissues, application of total parenteral feeding and parenteral administration of antimicrobial therapies do not only expand human life but also increase the number of susceptible patients to opportunistic infections. Immunodeficiency including the widely spread human immunodeficiency virus (HIV) infection and long-term peroral antibiotics administration enhance the susceptibility to systemic fungal infection, which is a great problem, due to its diagnostic difficulties. Therefore, prevention of systemic infections is extremely important, and accomplished by removal of predisposing factors as well as well-controlled objective drug administration (Noor, 2008).

This study provides data on species distribution of *Candida* isolated from patients' blood samples at a tertiary hospital over 18 years period, in which non-*albicans Candida* accounted for 79.9% of the total blood *Candida* isolates obtained throughout year 2001 to 2018, from which 160 out of 175 candidemia cases were not identified to species level during 2001-2002 until the introduction of API 20C AUX® kit for species identification. Our study has shown different scenario in the proportion of *Candida* species whereby *C. parapsilosis* predominates over *C. albicans*, in contrast to previous studies conducted in Malaysia and neighboring countries, where *C. albicans* was the major cause of candidemia (Tan *et al.*, 2016; Mohamed *et al.*, 2018).

In this study, *C. parapsilosis* was found to be the most common yeast isolated from blood specimens. The organism outnumbered *C. albicans* by 9.1% throughout 18 years, a trend not observed before in other Malaysian studies. Our finding also demonstrated the important role of non-*albican Candida* particularly *C. para-psilosis* as a cause of bloodstream infections in our health care setting. *C. parapsilosis*

was the most common species isolated from blood accounting for 29.2% of isolates, followed by *C. albicans* and *C. tropicalis*. The largest proportion of *C. parapsilosis* isolation was from intensive care units (both adults and pediatrics), while the smallest proportion were from surgical wards. These findings are in line with other published studies, where *C. parapsilosis* accounted for significantly more cases than *C. albicans* and *C. tropicalis* (Noor, 2008; Amalina, 2018). Similarly, the results of a population-based surveillance study in Barcelona, Spain indicated that *C. parapsilosis* isolates constituted 23% of all studied fungemia (Almirante *et al.*, 2006).

On the other hand, other studies have reported different findings, in which *C. tropicalis* was the most common *Candida* species isolated from blood (Tzar & Shamim, 2009; Ng *et al.*, 2015; Mohamed *et al.*, 2018). Santhanam *et al.* (2013) has reported *C. albicans* as the predominant species causing candidemia (33.9% of bloodstream isolates) in their setting (Santhanam *et al.*, 2013). In another study involving a total of 1062 *Candida* isolates, *C. albicans* accounted for 43.8% (n=465), followed by *C. parapsilosis* (26.5%), *C. tropicalis* (8.4%), *C. krusei* (5.8%), and *C. glabrata* (5.5%) (Kazak *et al.*, 2014). In a 16-year-study from Italy, *C. albicans* was reported to be the predominant species (44.2%) (Caggiano *et al.*, 2015). In a study from Taiwan, *C. glabrata* was shown to be the most frequently isolated non-*albicans Candida* species (Chi *et al.*, 2011). A multicenter study reported *C. albicans* as the predominant species, but its proportion was lesser than non-*albicans Candida* species collectively (Tan *et al.*, 2016).

The relative frequency of non-*albicans Candida* among *Candida* species in hospital-based studies done in various parts of the world seem to largely differ from 18.3% to 83.0%. This variability between various geographical regions is multifactorial, mostly due to different antifungal therapies and treatment practices, frequency of using invasive procedures such as use of indwelling catheters, patient demography and chronic underlying illnesses (Mohamed *et al.*, 2018).

Furthermore, species vary geographically in frequency of isolation, often because of different patient populations that may reflect differences in healthcare practices among different countries in the populations studied as well as differences in study methodologies adopted by different authors, or the systems for regular surveillance (Yapar, 2014; Caggiano *et al.*, 2015). This variability in the most frequent cause of candidemia has been explained partly by the high affinity of *C. parapsilosis* to intravascular devices and parenteral nutrition that were used widely in recent years (Almirante *et al.*, 2006).

The high profusion of *C. parapsilosis* could be clarified by factors related to hospital settings, such as gastrointestinal colonization, or the adhesion to intra-vascular devices and prosthetic materials. Additionally, *C. parapsilosis* has been known to be isolated from the hands of healthcare workers and is often responsible for nosocomial clusters, so its presence in hospital settings may be explained by insufficient implementation of infection control practices (Caggiano *et al.*, 2015). *C. parapsilosis* commonly colonize skin surface and has a better affinity to materials like acrylic in glucose-containing solutions and TPN solutions. It is obviously known to cause bloodstream infections in infants and neonates. The detection of *C. parapsilosis* in bloodstream infections indicates exogenous introduction of the pathogen from the surrounding environment (Giri & Kindo, 2012).

As has been expected in previous studies, non-*albicans Candida* continue to emerge as an important cause of serious disease in our health care setting by (Noor, 2008). Therefore, ongoing surveillance of serious infections caused by *Candida* species is important to track changes in the epidemiology and consequently in antifungal susceptibility among these emerging pathogens. In the present study, *C. parapsilosis* blood isolates were widely distributed across multiple hospital wards, in which intensive care units were the major sources accounting for 37% of the isolates collectively. Our results were in concordance with a previous study where *C. parapsilosis* were frequently isolated from intensive care settings and associated with high mortality rate (Liu *et al.*, 2018). A review of antifungal susceptibility profiles of *C. parapsilosis* in our setting revealed 94.4% of susceptibility to amphotericin B, 84.8% to fluconazole, 98.8% to voriconazole and 88.2% to caspofungin (data not shown). Thus, the results of this study support fluconazole as favorable antifungal drug for empirical and pre-emptive treatment of *C. parapsilosis* infections in our setting. Echinocandins has been recommended in azole-resistant *Candida* infections, whereas lipid formulation amphotericin B is recommended for patients with suspected azole- and echinocandin-resistant *Candida* infections (Tissot *et al.*, 2017; Bassetti *et al.*, 2018). Although the susceptibility of *C. parapsilosis* to currently available antifungal agents is generally predictable, antifungal susceptibility testing is strongly recommended because individual isolates of same species may not necessarily follow this general pattern.

CONCLUSION

In this 18-year study on *Candida* species blood isolates, a shift towards isolation of non-*albicans Candida* has been observed. Recently *C. parapsilosis* was noted to be the most predominant species. Continuous surveillance on the species prevalence and antifungal susceptibility profiles are needed to guide the clinicians in empirical and preemptive treatment of invasive candidiasis. Accurate epidemiology of invasive *Candida* infections is important to support institutional, national, and regional guidelines for the best management of invasive fungal infections.

Conflict of Interests

The authors declare that they have no conflict of interests.

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