Antifungal Susceptibility profile of Candida spp,causing candidemia in an Indonesian Tertiary Hospital

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Antifungal susceptibility profile of Candida spp. causing candidemia in an Indonesian tertiary hospital

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ABSTRACT

Introduction: Invasive candidiasis has emerged as a significant public health problem in recent years, and candidemia is the most common form. Identification of the *Candida* species is important since some *Candida* species showed an increasing trend of resistance to commonly used antifungal agents. This study was conducted to describe primary demographic data and the distribution of *Candida* species along with their antifungal susceptibility profiles among patients with candidemia.
Methods: We conducted a retrospective descriptive study on patients with candidemia and their *Candida* species identification and antifungal susceptibility testing (ID&AST) results at Dr. Kariadi Hospital, Indonesia, from January 2017 to December 2020. Identification and antifungal susceptibility testing of *Candida* species during these 4 years were determined using the Vitek-2 system. After collecting the data, it was analyzed by using SPSS 25.sav. The data was analyzed distributively, and was presented by table and barchart.
Result: A total of 85 *Candida* species were isolated from 74 patients. Infant age (58.10%) and intensive care (64.86%) patients contributed to most of the candidemia cases. The three most common *Candida* species isolated during the study period were *C. parapsilosis* (36.9%), *C. tropicalis* (25%), and *C. albicans* (25%). Among all *Candida* isolates, 98.9% were susceptible to Fluconazole and Voriconazole, 99% were susceptible to Caspofungin, Micafungin, and Flucytosine, 95.7 % were susceptible to Amphotericin B. Echinocandin resistance emerged in 2020 from a *C. glabrata* isolate.
Conclusion: The present study, conducted in a tertiary care Indonesian hospital, showed the predominance of non-*albicans Candida* with favorable antifungal susceptibility profiles.

Keywords: Antifungal susceptibility, *Candida*, Candidemia
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INTRODUCTION

Along with advancing number of critical patients receiving broad spectrum antibiotics, immunosuppressants, and invasive devices, invasive candidiasis has emerged as a significant public health problem.[1,2] Significant mortality rates are seen among invasive candidiasis patients in both children and adult groups.[3,4] Among hospitalized patients, candidemia is the most common form of invasive candidiasis.[5] Of all different *Candida* species causing candidemia, *C. albicans, C. glabrata, C. tropicalis, C. parapsilosis* and *C. krusei* are the most common isolated species.[6]

The predominance of *albicans* and non-*albicans Candida* varies across the globe.[7–9] A shift from a predominance of *Candida albicans* toward a predominance of non-*albicans Candida*, especially *C. glabrata, C. parapsilosis*, and *C. tropicalis* was documented.[9] While *Candida albicans* resistance to fluconazole, the primary therapeutic option in candidemia, is regarded as low (0.5-2%), resistance of non-*albicans Candida* to fluconazole is higher. Specific species, *C. krusei*, is even intrinsically resistant to fluconazole.[10]

Regular survey on the distribution of *Candida* species and their antifungal susceptibility profiles is needed to acknowledge the predominant species, to be aware of the emergence of antifungal resistant strains, and to guide the empiric therapy of *Candida* infection. This study aimed to describe *Candida* species' distribution along with their antifungal susceptibility profiles among patients with candidemia in a tertiary care hospital in Indonesia.

METHODS

This study was conducted at Dr. Kariadi Hospital, Semarang, Indonesia. The facility is one of the tertiary care hospitals in Indonesia, which have 1175 beds in total, and 103 beds of them were dedicated to intensive care. It is also a referral hospital

for Central Java Province, the third most populated province in Indonesia.

We retrospectively reviewed candidemia cases and their *Candida* species identification and antifungal susceptibility testing (ID&AST) results at Dr. Kariadi Hospital, from January 2017 to December 2020. All patients with at least one positive blood culture isolating *Candida* species with clinical and laboratory biomarkers suggesting fungal infection were included. Data on patients' characteristics (age, sex, ward) was collected through hospital electronic medical records.

The following blood culture steps are routinely performed in the facility. Blood culture from any patient is performed in an automated blood culture system (BD BACTEC). Bottles giving positive signal are Gram stained and subsequently cultured onto relevant solid media. Bottles giving no signal of growth are incubated for 5x24 hours before being discarded. Isolated colony(es) are then Gram stained and subjected to the next testing step, i.e., ID&AST using Vitek-2 system. For colonies of yeasts, the Vitek Yeast Biochemical and Vitek 2 ID-YST card are used. There was a particular phase during the study period when only the Vitek Yeast Biochemical Cards were available in our facility without the Vitek 2 ID-YST card, thus AST on isolated *Candida* was not performed during this period.

Patients' characteristic data (age, sex, ward) was retrieved from electronic medical records. In this study, we present patients' characteristic data, and the distribution and antifungal susceptibility profile of *Candida* in tables, graphics, and narration.

After collecting the data, it was analyzed by using SPSS 25.sav. The data was analyzed distributively, and was presented by table and barchart. This study showed the frequency and percentage of each variable.

RESULTS

From January 2017 to December 2020, 84 *Candida* species were isolated and identified from 74 patients. AST results were available in 69 of these 84 isolates. AST was not performed in the 15 isolates due to unavailability of the Vitek 2 ID-YST card.

Candidemic patients' characteristics are described in Table 1. The female gender predominated candidemia cases in 2017 dan 2018, but the male gender contributed more cases in 2020. Infant patients were predominant over the study period, accounting for more than half of all candidemia cases. Furthermore, patients in intensive care units (64.87%) accounted for a significant proportion of cases compared to patients in non-intensive care units.

Out of the 84 isolates, *C. parapsilosis* (n= 31, 36.9%) was the most common, and followed by *C. tropicalis* (n=21, 25%) and *C. albicans* (n=21, 25%). *C. glabrata, C. famata, C. haemulonii, C. krusei, C. pelliculosa* were the other species of *Candida,* accounting for much smaller proportions (Table 2). Furthermore, Since the first year of the present *Candida* surveillance in 2017, non-*albicans Candida* has always been predominant in causing candidemia (Figure 1).

Of 84 *Candida* species isolates, 69 had antifungal susceptibility test results. The summary of these isolates' antifungal susceptibility profile is described in Table 3. Resistance to any antifungal in the Vitek-2 panel has occurred since the start year of the present surveillance. However, only 5 out of 69 isolates (7.25%) showed resistance to any antifungal tested (Table 4). Two isolates of *C. haemulonii* were resistant to amphotericin B, and one of them also resistant to both fluconazole and voriconazole. One isolate of *C. glabrata* was resistant to caspofungin and micafungin, and one isolate of *C. krusei* was resistant to flucytosine. Only one out of 17 isolates of *C. albicans* showed resistance to any antifungal tested, amphotericin B. Distribution of these resistant isolates and their isolation year is described in Table 4.

Table 1. Distribution of patients with candidemia over the study period

Category	2017	2018	2019	2020	Cumulative
Sex					
Male	5	8	8	14	35 (47.29%)
Female	8	14	8	9	39 (52.71%)
Age					
Infants (0-1 y.o)	7	12	10	14	43 (58,10%)
Children (2-10 y.o)	2	2	1	1	6 (8.10%)
Adolescent (11-19 y.o)	0	1	1	1	3 (4.05%)
Adult (20-60 y.o)	3	5	3	5	16 (21.62%)
Elderly (>60 y.o)	1	2	1	2	6 (8.10%)
Ward					
Non-Intensive Care Unit	6	11	6	13	26 (35.13%)
Intensive Care Unit	7	11	10	10	48 (64.87%)

Table 2. Distribution of *Candida* species over the study period

Candida isolates	Number of Isolates	Percentage
C. parapsilosis	31	36,90
C. tropicalis	21	25,00
C. albicans	21	25,00
C. glabrata	5	5,95
C. famata	2	2,38
C. haemulonii	2	2,38
C. krusei	1	1,19
C. pelliculosa	1	1,19

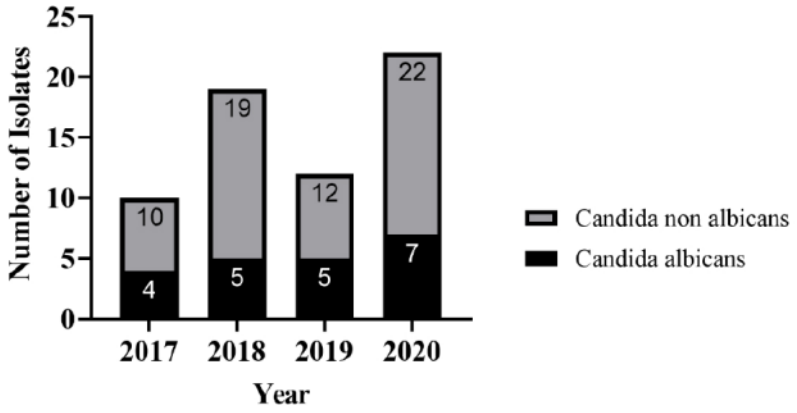

Figure 1. Composition of *C. albicans* and non-*albicans Candida* over the study period

Table 3. Antifungal susceptibility profile of isolated *Candida* species

Species of *Candida*	Susceptibility (%, number of isolates)					
	Fluconazole	Voriconazole	Caspofungin	Micafungin	Amphotericin B	Flucytosine
C. albicans	100 (17)	100 (17)	100 (17)	100 (17)	**88.2 (17)**	100 (16)
C. parapsilosis	100 (24)	100 (24)	100 (24)	100 (24)	100 (24)	100 (24)
C. tropicalis	100 (17)	100 (17)	100 (17)	100 (17)	100 (17)	100 (17)
C. glabrata	100 (3)	100 (4)	**75 (4)**	**75 (4)**	100 (4)	100 (3)
C. haemulonii	**0 (1)**	**0 (1)**	100 (1)	100 (1)	**0 (1)**	100 (1)
C. duobushaemulonii	-	100 (1)	-	-	**0 (1)**	100 (1)
C. krusei	-	100 (1)	**0 (1)**	100 (1)	100 (1)	**0 (1)**
C. pelliculosa	100 (1)	100 (1)	100 (1)	100 (1)	100 (1)	100 (1)

-: not applicable

Table 4. Distribution of *Candida* sensitivity profile in 5 resistant isolates found in the present study

Isolate (year)	Fluconazole	Voriconazole	Caspofungin	Micafungin	Amphotericin B	Flucytosine
C. albicans (2017)	S	S	S	S	R	S
C. haemulonii (2018)	R	R	S	S	R	S
C. duobushaemulonii (2019)	-	S	-	-	R	S
C.krusei (2020)	-	S	I	S	S	R
C. glabrata (2020)	-	S	R	R	S	S

S: susceptible; R: resistant; -: not applicable

DISCUSSION

The Candida species is one of the commensal organisms that colonize the skin and mucosal surfaces, which can cause disease in immunocompromised individuals. Infections caused by *Candida Sp* can be classified into mucocutaneous and invasive candidiasis. Mucocutaneous candidiasis consists of oropharyngeal candidiasis, esophageal candidiasis, and vaginal candidiasis. Meanwhile, invasive candidiasis consists of infections of deeper organs, with the most common form being candidaemia.[2,5]

The results of this study showed that more than half of the total candidaemia cases in Dr. Kariadi come from infant patients, especially newborns. Candidiasis poses an increased risk in the newborn population due to an immature immune system influenced by health care, such as central venous catheters, broad-spectrum antibiotics, and parenteral nutrition.[2] In this study, nearly two-thirds of cases occurred in the intensive care ward. This is in line with a prospective multicenter case-control study involving six teaching hospitals in Switzerland and France. The study demonstrated that the ICU population was an independent risk factor for candidaemia, including patients receiving total parenteral nutrition, acute kidney injury, heart disease, previous septic shock, and exposure to aminoglycoside antibiotics.[11] In the present study, we did not assess the risk factors for contracting candidemia in our patients.

The three most common Candida species found in the isolates of candidemia patients at Dr. Hospital. Kariadi. are *C. parapsilosis* (36.9%), *C. tropicalis* (25%) and *C. albicans* (25%). The predominance of Candida non-albicans has occurred since our surveillance period in early 2017. Cipto Mangunkusumo, a tertiary care hospital and a national referral hospital in Indonesia. During 2011-2014, *C. tropicalis* and *C. parapsilosis* accounted for up to 60%, while *C. albicans* only accounted for 25% of candidaemia cases at Dr. Hospital. Cipto Mangunkusumo.[12] Meanwhile, in the last few decades, *C. albicans* was recorded as the most common species causing most cases of candidiasis. It is also found in cases of candidemia in other countries. A large, laboratory-based surveillance study covering 25 hospitals in China, Hong Kong, India, Singapore, Taiwan, and Thailand that collected data from 2010-2011, showed that the most frequently isolated Candida species in candidaemia was *C. albicans* (41,3%).[13] However, when compared with previous decades, there has been a gradual shift from dominant *C. albicans* to non-albicans Candida. Non-albicans Candida species have been reported to be a major cause of opportunistic fungal infections.[7,14]

The finding of the dominance of *C. parapsilosis* in Dr. Hospital. Kariadi is in accordance with the results of previous studies, which showed that *C. parapsilosis* was more commonly found in southern Europe, Asia, and South America, while *C. glabrata* was more frequently found in northern Europe, the United States, and Canada.[15] *C. parapsilosis* is the most common human commensal pathogen, often isolated from the hands. This was associated with the finding that carriers of *C. parapsilosis* came from health care workers and other patient pathogens through molecular typing methods.[16] Therefore, maintaining hand hygiene is very important for preventing outbreaks of *C. parapsilosis* infection.

In the present study, among all *Candida* isolates, 98.9% were susceptible to Fluconazole and Voriconazole, 99% were susceptible to Caspofungin, Micafungin, and Flucytosine, and 95.7% were susceptible to Amphotericin B. Only five isolates out of 69 isolates that had antifungal susceptibility test results were resistant to any antifungal tested. The use of fluconazole as the empirical therapy for candidemia suspicion appears to be still valid, although continuous surveillance and fungal ID&AST are still warranted. As a tertiary hospital, the administration of fluconazole in Dr. Kariadi Hospital is thought to be higher than in other smaller hospitals. Nevertheless, the resistance to fluconazole was very low in the present study. Factors other than antifungal pressure contributing to acquired resistance to azole and other antifungals have yet to be elucidated.

Echinocandin-resistant Candida species are emerging worldwide among the most clinically relevant Candida species, but the most frequently found resistant is *C. glabrata*.[17] Isolation of emerging multidrug-resistant opportunistic pathogens *C. haemulonii* and *C. duobushaemulonii* and also *C. krusei* and *C. glabrata* in the present study warrants continuous surveillance and accurate fungal ID&AST.

The limitation of this study is that it has not discussed the risk factors that can cause candidaemia in newborn patients. Therefore, further research is needed to determine the specific risk factors that contribute to the incidence of candidaemia in Dr. Hospital. Kariadi still has to be explained.

CONCLUSION

From 2017-2020, non-*albicans Candida* contributed a significant proportion as the causes of candidemia (75%) in Dr. Kariadi Hospital. The three leading causes of candidemia were *C. parapsilosis, C. tropicalis,* and *C. albicans*. *Candida* species isolates were 95.7 % susceptible to Amphothericin B, 98.9% susceptible to Fluconazole and Voriconazole, 99% Susceptible to Flucytosine, Caspofungin, and Micafungin.

DISCLOSURE

Conflict of Interest

All authors declared that there is no conflict of interest regarding this publication

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This study was self-funded without any contribution from a third party.

Author Contribution

All authors contributed equally in the writing of this article

Ethic Approval

This study had been ethically approved by ethical commission of Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia

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