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Characteristics of candidiasis patients and *Candida* species antifungal sensitivity patterns in tertiary referral hospitals, Indonesia

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ABSTRACT

Introduction: Candida species causes opportunistic infections, such as candidiasis, in patients with compromised immune systems and people receiving long-term antibiotics treatment. The use of antifungals causes resistance. Hence, it is necessary to know the antifungal sensitivity pattern of these organisms, which must be considered in definitive therapy. Therefore, this study aims to determine the characteristics of people with candidiasis and the antifungal sensitivity pattern of Candida species isolates in patients at Prof. Dr. IGNG Ngoerah Hospital, Denpasar, Indonesia.

Method: This is a retrospective descriptive study using secondary data from isolates of Candida species that were isolated and identified with the Vitek2® Compact system (bioMérieux, France). The experiment was carried out at the Clinical Microbiology laboratory of Prof. Dr. IGNG Ngoerah Hospital from February 1 to July 30, 2020.

Results: A total of 87 Candida species were isolated based on gender, where 55.2% and 44.8% were found in males and females, respectively. Furthermore, the most common isolate was Candida albicans, which accounts for 48.3% of the total microbes. Approximately 41.1% of Candida species were found in the sputum specimens. Furthermore, these species are 100% 98.9% and sensitive to Flucytosine and Micafungin, respectively, while 97.7% and 93.1% sensitivity was recorded for Caspofungin, Voriconazole, Amphotericin B and Fluconazole. Candida species were found in patients with diabetes mellitus and malignancy. They were also observed after using antibiotics for prophylactic, empirical and definitive therapy.

Conclusion: The dominant Candida species found was Candida albicans. Characteristics of candidiasis patients were found in people with diabetes mellitus, malignancy and the use of antibiotics in prophylactic, empirical and definitive therapy. Infections caused by these organisms need to be considered in administering antifungal therapy to prevent resistance.

Keywords: Candida species, Comorbid, Antibiotics, Antifungal Sensitivity.
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INTRODUCTION

Candidiasis caused by Candida is a common secondary infection in immunocompromised people, and its synonyms include candidosis, moniliasis, or thrush. Furthermore, it is often found in the oral cavity, digestive tractus or other body parts. *Candida* is in the form of yeast.[1] *Candida* species, such as Cryptococcus, Aspergillus and Pneumocystis, are the major cause of fungal infections and global health problems.[2,3] Candidiasis can occur locally as well as spread hematogenously. The localized form often occurs as erythema and white plaque in moist skin folds (diaper rash) or on mucosal surfaces (oral thrush). The disease also occurs in the deep tissues, and it is very common among immunocompromised individuals.[4] Primary candidiasis can manifest in airway aspiration and secondary infection due to hematogenous spread.[5]

Candida species is a normal flora in the human body found on the skin, mucous membranes and digestive tract, but can cause superficial and deep fungal infections.[6] The fungi can also be found on the ground. Candida spp. are often found in human and animals.[7] Most of diseases caused by *Candida* spp. are found throughout the world in the mucosa and body system. They can be divided into superficial, cutaneous, mucosal, and systemic infections.[8]

In a previous study in China, antifungal sensitivity patterns found *Candida* spp. IncludingIncluding *Candida albicans, Candida parapsilosis*, *Candida tropicalis, Candida glabrata sensu stricto*, *Candida guilliermondii, Candida pelliculosa*, *Candida krusei*, *Candida lusitaniae*, *Candida haemulonii*, were discovered.[9] In Indonesia study found an antifungal sensitivity pattern, the isolates of *Candida* spp, including *C. parapsilosis, C. tropicalis*, *C. albicans, C. glabrata, Candida famata*, *C. haemulonii*, *C. krusei* and *C. pelliculosa,* were discovered.[10]

Candida species causes opportunistic infections in patients with compromised immune systems and people receiving long-term antibiotics treatment.[11] These conditions occur in individuals due to comorbid diseases include Human Immunodeficiency Virus (HIV),

organ transplant, malignancies and immunosuppressant treatment patients,[12] blood malignancy, acute necrotizing pancreatitis, liver, heart and kidney transplantation, also influenced by environmental factors, such as habitats and the presence of colonization,[13] Diabetes Mellitus (DM), bronchial asthma, other malignancy, Chronic Obstructive Pulmonary Disease (COPD), pregnancy,[14] prolonged use of antibiotics and the presence of other secondary infections.[15]

The clinical diagnosis of this condition is non-specific because it is caused by different organisms, comorbid disease or complications from treatment. Furthermore, it depends on an objective assessment of the response to antifungal treatment and the specimens collection of specimens conforms to the microbiological laboratory and test procedures standards.[12]

Treatment of fungal infections includes the use of azole, polyenes, echinocandin and flucytosine.[16] The use of antifungals infection therapy needs to be considered to prevent resistance due to their limited antifungal drugs.[17] Based on the description, this study aims to determine the isolates of Candida spp., their antifungal sensitivity pattern and characteristics of candidiasis in patients at Prof. Dr. IGNG Ngoerah Hospital, Denpasar.

METHODS

This is a descriptive retrospective study with secondary data, carried out at the Clinical Microbiology Installation of Prof. Dr. IGNG Ngoerah Hospital, Denpasar. Isolates of *Candida* spp. were obtained from clinical specimens of patients. The secondary data include sputum samples, tube sputum, urine, and blood. The specimen culture was performed on a Sabouraud Dextrose Agar (SDA) with incubation at 37°C. Subsequently, the isolates were identified and tested for antifungal sensitivity using an automatic Vitek 2 Compact® machine (Biomereux, France).[18] The results were secondary data collected for six months from February 1 to August 31, 2020. The other data include gender, comorbidities and duration of antibiotics use.[14,15] Inclusive criteria were the results of antifungal sensitivity tests on *Candida* spp., completed with flucytosine, fluconazole, voriconazole, amphotericin B, caspofungin and micafungin. The exclusion criteria include incomplete antifungal sensitivity tests and double specimens. After collecting secondary data, they were statistically analyzed using SPSS version 25.0. The data analysis results are presented in the form of narratives, figures and tables.

RESULTS

From February to December 2020, a total of 87 Candida spp., which met the inclusion criteria were isolated. The characteristics of study subjects were determined by grouping the test organism. Based on sex, 48 males and 39 females accounted for 55.2% and 44.8% of the population, respectively. Candida species were found in sputum specimens 41.1%, sputum Endotracheal Tube (ETT) 14.9%, urine 29.9%, blood 11.5% and others samples 2.3%, respectively. *Candida albicans was* the most common species found in approximately 48.3% of the isolates, as shown in Figure 1.

The result showed that 42.5% of candidiasis characteristics were found in patients with comorbid diseases, including DM, malignancy, followed by DM and Hypertensive Heart Disease (HHD). A total of 80 (92%) respondents used antibiotics in prophylactic, empirical and definitive therapy, as shown in Table 1.

In the antifungal susceptibility test, 100% and 98.9% of *Candida* spp. were

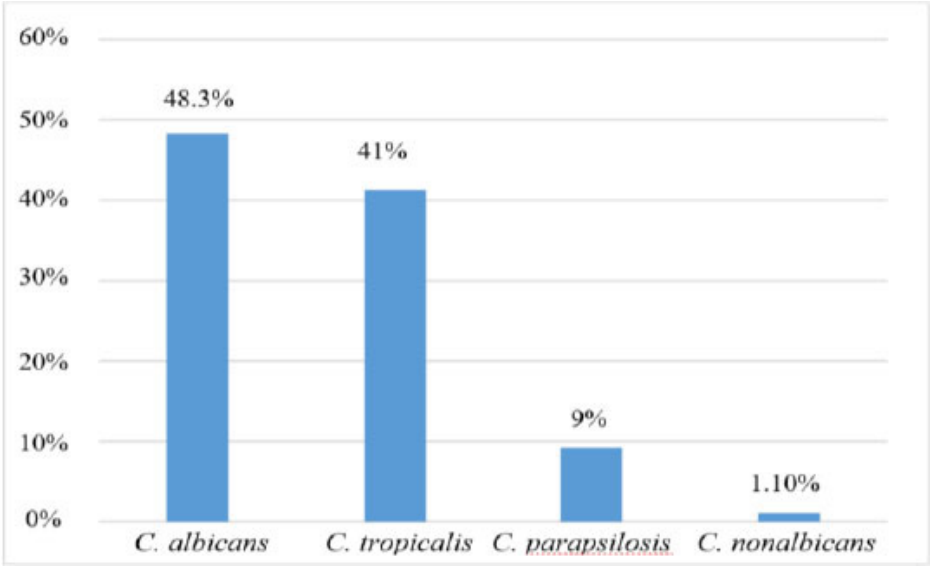

Figure 1. Distribution of Candida species.

Table 1. Characteristics of Study Subjects Based on Comorbidities and Use of Antibiotics.

Variable	Total (%) (n=87)
Comorbid	
DM	12 (13.8)
Malignancy (Acute Myeloid Leukemia, *malignant lymphoma*, cervix cancer, rhabdomyosarcoma, nasopharynx cancer)	7 (8)
DM and HHD	5 (5.7)
HHD	4 (4.6)
DM and Chronic Kidney Disease (CKD)	3 (3.4)
CKD	3 (3.4)
HIV	1 (1.1)
Hormonal Disorder	1 (1.1)
Duration of use antibiotics	
1-2.5 days	39 (44.8)
3-5 days	15 (17.2)
≥7 days	26 (29.9)

Table 2. Candida Species Sensitivity to Antifungals.

Antifungals	R (%)	S (%)
Fluconazole	6.9	93.1
Voriconazole	2.3	97.7
Micafungin	1.1	98.9
Caspofungin	2.3	97.7
Amphotericin B	2.3	97.7
Flucytosine	0	100

sensitive to flucytosine and micafungin, respectively, as shown in Table 2.

DISCUSSION

In this study, 48.3% of the isolates were C. albicans, which according to Montes et al, where 41.2% the most reported and cause human infection.[18] Furthermore, Suhartono et al who recorded 30.88%.[19] The result showed that 41.4% of isolates found in the sputum specimen was Candida spp., according to Masuoka et al with the prevalence of 40.6%.[20] C. albicans colonizes the respiratory tract in patients with pneumonia[21] and causes candidiasis with the prevalence of 52%.[22] The type of sample needed for microbiological testing is very important, which can cause errors in the interpretation of culture results as well as misdiagnosis.[23]

In this study, Candida spp. was often isolated in patients with comorbidities, namely DM, malignancy, HHD, CKD and HIV. The presence of diabetes mellitus with uncontrolled glucose levels is a carbon source that plays an important role in the growth of these species.[24,25] Diabetes mellitus changes in the immune system, which make its patients more susceptible to fungal infections.[26] Candida species was also found in patients with comorbidities including malignancies, such as Acute Myeloid Leukemia (AML), malignant lymphoma, cervical cancer, rhabdomyosarcoma and nasopharynx cancer. Candida species in people with malignancies, such as oral cavity carcinomas, stomach and esophageal carcinomas, lymphoma malignant, cervical cancer, Chronic Myeloid Leukemia (CML), bone tumors, bladder cancer and colon cancer. The occurrence of infection along with malignancy causes invasive infection and candidemia.[27] Furthermore, Candida spp. isolates in patients with other malignancies, including head, neck and blood cancer.[28] In patients with CKD, uremia is characterized by immunodepression[29] and decreased macrophage activity for phagocytosis.[30] In human immunodeficiency virus patients, Candida spp. colonize the oral cavity and significantly cause candidiasis.[31]

This study revealed their presence after the use of antibiotics for 1-2,5 days as prophylactic, 3-5 days as empirical and >7 days as definitive therapies. Exposure to antibiotics is a risk factor for Candida infection.[32] Antibiotics can inhibit the growth of bacteria, but they do not affect the growth of Candida. Treatment of bacterial infections with antibiotics induced the growth of C. albicans, which is a normal flora, hence, it was present in the culture results.[33] The duration of administration depends on the ability of the drug to kill the causal bacteria based on the patient's clinical diagnosis. When there is no clinical improvement, it is necessary to re-evaluate the use of antibiotics and the accuracy in diagnosing infection.[34]

Treatment of candidiasis depends on the availability of antifungal drugs. The sensitivity test of Candida spp. to flucytosine showed that it was 100% sensitive, and this was lower than the result of Terças et al, 92% sensitive.[35] Flucytosine is rarely used in Indonesia compared to fluconazole, which is very common in therapy. In this study, the sensitivity of fluconazole was 93.1%, and this was similar to the result of Wang et al more than 90% sensitive.[36] Meanwhile, previous study reported a lower sensitivity of 71.5%. *Candida* infection treatment is often carried out based on the type and site infections as well as pattern of antifungal sensitivity of *Candida* spp.[6] Patients with DM and HIV are at high risk for azole resistance, which are the main choice. The host immune system and antifungal drugs play an important role in successfully treating fungal infections. Furthermore, these species have also acquired resistance to echinocandin, flucytosine and polyenes. Azole group cannot be used for *Candida* spp. in people with HIV usually receive long term therapy, which can cause resistance.[37]

Intrinsically resistance *Candida* spp. can cause resistance to fluconazole.[38] Overexpression of efflux pump leading to azole resistance found in *C. albicans*.[39] *Candida albicans* isolates resistance to echinocandins can occurred point mutations FKS1 and *FKS2* with decreased glucan synthesis.[40] *Candida parapsilosis* isolates resistance to fluconazole could be caused by overexpression of *CDR1, MDR1, ERG11*.[41] *Candida tropicalis* isolates resistance to fluconazole could be due to expression of the *ERG11* gene.[42] Point mutations in *ERG3* and *ERG6* can cause polyenes resistance.[40]

limitations of this study, type of Candida species isolates was not described for respective sensitivity to antifungals. Therefore, further study is needed with a larger number of isolates.

CONCLUSION

In this study, the isolates of *Candida* spp. were frequently found in the sputum specimens. Candidiasis patients' characteristics were observed after using prophylactic, empiric, and definitive antibiotics. Furthermore, *Candida* spp. is often found in patients with diabetes and malignancy. Antifungals sensitivity test include flucytosine, followed by voriconazole, micafungin, caspofungin, amphotericinB and fluconazole, which can still be used in definitive therapy at tertiary referral hospitals.

DISCLOSURES

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This research was conducted without the involvement of a third party.

Conflict of Interest

All authors declare there is no conflict of interest related to this publication.

Author Contribution

All authors contributed equally in this study.

Ethics Approval

The ethical commission had ethically approved this study of the Faculty of Medicine, Universitas Udayana, Bali, Indonesia.

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