Althea Medical Journal
ISSN Online: 2337-4330
https://doi.org/10.15850/amj.v11n3.3351

Original Article

Prevalence and Resistance Patterns of *Candida albicans* in Diabetic and Non-Diabetic Patients with Urinary Tract Infections

Christian Prijana, Ida Parwati, Delita Prihatni
Department of Clinical Pathology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Abstract

Background: *Candida spp.* is an opportunistic fungi genus that can turn into pathogens, especially in those with inadequate immune response such as in patients with diabetes mellitus (DM), of which *Candida albicans* is the most common species. This study aimed to determine the prevalence and antifungal resistance patterns of *Candida albicans* in DM and non-DM patients with urinary tract infections (UTIs).

Methods: A retrospective descriptive observational study was conducted in 2023 using medical record data of DM and non-DM patients with UTIs who were treated at a tertiary hospital in Bandung, Indonesia from July 2019 to December 2021. Data on patient characteristics, proportion of fungal species causing UTI, and antifungal resistance patterns of *Candida albicans* were presented in tabular form and chart.

Results: Of a total 291 patient data, 21 were DM patients and 270 were non-DM patients, mostly were female, 71.4% and 58.2%, respectively. The prevalence of *Candida albicans* in DM patients was 66.7% and in non-DM patients was 70.7%, mostly resistant to micafungin (7.1% and 8.9%, respectively.

Conclusion: Female is more susceptible to UTIs. More than half of DM and non-DM patients with UTIs are infected with *Candida albicans*, and mostly resistant to micafungin. Antifungal treatment guidelines based on resistance patterns and education on personal hygiene to prevent UTIs are recommended.

Keywords: Antifungal, *Candida albicans,* diabetes, resistance, urinary tract infections

Althea Medical Journal.
2024;11(3):158–163

Received: July 20, 2023
Accepted: September 3, 2023
Published: September 30, 2024

Correspondence:
Christian Prijana
Department of Clinical Pathology, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital
Jl. Pasteur No 38 Bandung, Indonesia

E-mail:
chrkero@gmail.com

Introduction

Candida is a genus of opportunistic fungi that can be pathogenic to immunodeficient patients. *Candida spp.* is one of the main causes of morbidity and mortality in the world and is a challenge for public health. The frequency of *Candida spp.* infection can reach 15% of total patients in hospitals, and 50–70% of all existing fungal infections.[1]

Candida albicans is the fungal species most commonly found in isolates taken from hospitalized patients.[2] However, nowadays, other *Candida* species such as *Candida glabrata, Candida tropicalis, Candida parapsilosis, Candida krusei, Candida famata, Candida guilliermondii,* and *Candida lusitaniae* findings also starts to increase, especially in patients infected with human immunodeficiency virus (HIV).[1]

In order to effectively form colonies on its host, the genus Candida must be able to adapt using various signaling pathways to several external stresses such as temperature, oxygen, pH, carbon dioxide, carbon sources, nutrient availability, the immune system, and other microorganisms present in the host tissues. In patients with immunodeficiency or diabetes mellitus, the immune response produced is inadequate to inhibit the growth of those organisms, thus making the environment more susceptible to the organism and making

it easier for *Candida spp.* to spread and cause disease that is often fatal to the patients.[3]

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia.[4] This disorder can be caused by decreased secretion of insulin, tissue resistance to insulin, or both. The International Diabetes Federation (IDF) in 2015 has stated that around 415 million people aged 20–79 years worldwide experience DM. This issue will become a global burden and it is predicted that sufferers will increase by 200 million by 2040.[5]

Chronic hyperglycemia can cause damage to multiple organ systems, which can lead to various life-threatening complications, such as microangiopathy (retinopathy, nephropathy, neuropathy), and macroangiopathy which can increase the risk of cardiovascular disease two to fourfold.[5]

In patient with DM, treatment of fungal infections can be inadequate due to changes in the pharmacokinetics and pharmacodynamics of antifungal drugs.[6] Pharmacokinetics is the process of drug absorption in the body, biotransformation, distribution of drugs and their metabolites in tissues, to elimination of drugs and their metabolites into the body, whereas pharmacodynamics is a series of drug activities in the body, including reactions with target cells, to the biochemical and physiological consequences of these reactions.[7] DM inhibits the action of antifungal drugs by slowing drug absorption and gastric emptying.[8] DM also results in glycation of albumin which decreases albumin's affinity for drugs thereby increasing the levels of drugs that are not protein-bound in the blood. Ultimately, this disrupts the distribution of antifungal drugs because most antifungal drugs must bind to albumin to be distributed.[9] Distribution to peripheral tissues will also be disrupted due to microvascular damage and decreased capillary permeability in DM patients.[8]

DM can also cause diabetic hepatosclerosis which will decrease liver function such as albumin production which can interfere with drug distribution, as well as drug biotransformation.[8] This is caused by liver inflammation induced by high glucose levels in the blood.[10] These pharmacokinetic and pharmacodynamic changes can increase resistance to antifungals.[11]

DM patients are more susceptible to urinary tract infections (UTIs) including those caused by fungi, due to several mechanisms, such as increased adhesion of pathogens due to damage to uroepithelial cells, impaired bladder contractions resulting in urinary stasis which will later become the perfect site for pathogen growth and urine containing a lot of glucose will facilitate the growth of pathogens.[12] Thus, the rate of antifungal resistance in the DM patient group could be higher than the non-DM patient group. Therefore, this study aimed to determine the prevalence and antifungal resistance patterns of C. albicans in DM and non-DM patients with UTIs.

Methods

This study was a retrospective descriptive observational study conducted in 2023 at the Clinical Pathology Laboratory at Dr. Hasan Sadikin General Hospital Bandung, Indonesia. Data on patients diagnosed with UTIs admitted at Dr. Hasan Sadikin General Hospital Bandung from July 2019–December 2021 were collected and grouped into patients with or without DM. Patients with HIV infection with or without acquired immune deficiency syndrome (AIDS) were excluded from this study.

In brief, data of urine culture with positive fungi and routine urine examination as well as random blood glucose levels on the same day as taking specimens for urine culture were gathered. Samples for urine culture were taken from patients' random mid-stream urine. Culture was performed using blood and MacConkey agar. Identification of microorganisms and antifungal susceptibility were performed using an automated identification and susceptibility testing system using fluorescence-based technology. The antifungals used were fluconazole, voriconazole, caspofungin, micafungin, amphotericin B, and flucytosine.

Blood glucose levels were measured from patients' serum taken by trained phlebotomists. Samples were incubated in room temperature for 30 minutes after phlebotomy and then centrifuged for 10 minutes at speed of 1,300 g (2,600 RPM) using swing-out rotors. Patients' serum glucose levels were assayed using an automated spectrophotometric chemistry analyzer in less than 4 hours after phlebotomy. DM status was set when random blood glucose levels were more than 200 mg/dL.

Patients' characteristics, the proportion of fungal species that ausing UTIs, and the antifungal resistance patterns of *C. albicans* in DM and non-DM patients were analyzed using Microsoft Excel 2019 and presented in tabular form and chart. Ethical approval was granted by the Research Ethics Committee of Dr. Hasan

Table 1 Characteristic of DM and non-DM Patients with Urinary Tract Infections

Characteristics		Number of Patients	
		DM (n=21) n (%)	Non-DM (n=270) n (%)
Gender	Male	6 (28.6)	113 (41.9)
	Female	15 (71.4)	157 (58.2)
Age (years)	<1	-	19 (7.0)
	1–4	-	17 (6.3)
	5–14	1 (4.8)	21 (7.8)
	15–24	-	28 (10.4)
	25–34	-	19 (7.0)
	35–44	-	36 (13.3)
	45–54	5 (23.8)	30 (11.1)
	55–64	7 (33.3)	32 (11.9)
	65–74	4 (19.0)	46 (17.0)
	>75	4 (19.0)	12 (4.4)
Comorbid diseases	Hypertension	5 (23.8)	54 (20.0)
	Congestive heart failure	1 (4.8)	11 (4.1)
	Dyslipidemia	2 (9.5)	51 (18.9)
	Coronary artery disease	-	8 (3.0)
	Peripheral artery disease	1 (4.8)	9 (3.3)
	Chronic kidney disease	1 (4.8)	30 (11.1)
	Cerebrovascular accident	1 (4.8)	6 (2.2)
	Malignancy	-	42 (15.6)
	Autoimmune diseases	-	23 (8.5)
	Tuberculosis infection	1 (4.8)	24 (8.9)

Note: DM=Diabetes mellitus, Non-DM= non-diabetes mellitus

Sadikin General Hospital Bandung, Indonesia (Letter no. LB.02.01/X.6.5/379/2022).

Results

Of the total 291 patient data, 21 were DM patients and 270 were non-DM patients, mostly were female, 71.4% and 58.2% respectively. The number of female patients was more than male patients in both the DM and non-DM groups (71.4% and 58.2%).

The age group most affected by fungal infections in the urinary tract in the DM group was 55–64 years (33.3%), meanwhile in the non-DM group it was 65–74 years (17.0%). The most common comorbidity found in fungal UTIs patients in each group was hypertension, at 23.8% and 20.0%, respectively, as shown in Table 1.

All fungal UTIs found in this study were caused by the genus Candida and Candida albicans was the most common fungal species

Table 2 Distribution of Fungal Species Found in DM and Non-DM Patients with Urinary Tract Infections

Species	DM Patient (n=21) n (%)	Non-DM Patient (n=270) n (%)
Candida albicans	14 (66.7)	191 (70.7)
Candida tropicalis	3 (14.3)	31 (11.5)
Candida parapsilosis	2 (9.5)	26 (9.6)
Candida glabrata	1 (4.8)	20 (7.4)
Candida krusei	1 (4.8)	2 (0.7)

Note: DM=Diabetes mellitus, Non-DM= non-diabetes mellitus

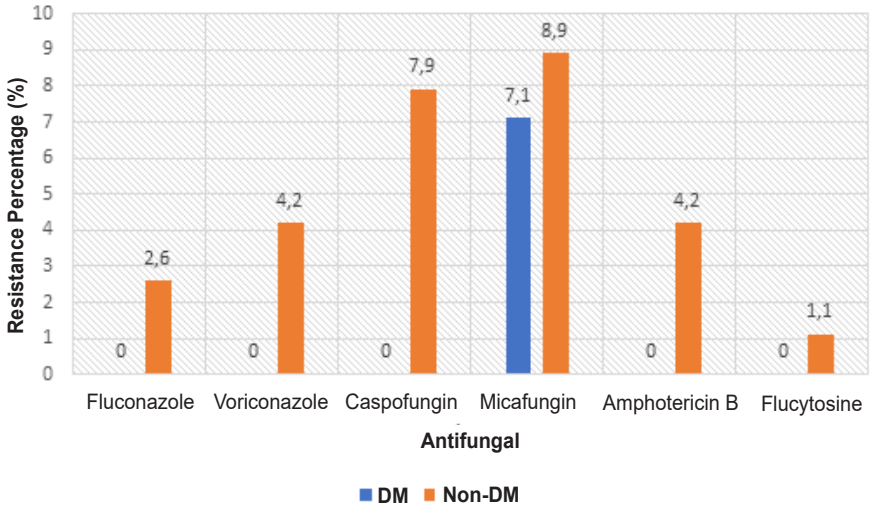

Figure 1 Resistance Patterns of *Candida albicans* in DM and Non-DM Patients

in DM patients (66.7%) and in non-DM patients (70.7%) (Table 2). In the DM patients group, *C. albicans* was resistant to micafungin (7.1%); whereas in the non-DM patient group, *C. albicans* resistance was most common to the antifungal's micafungin (8.9%) and caspofungin (7.9%) as depicted in Figure 1.

Discussion

This study has shown that the distribution of fungal UTIs is more prevalent in women. This is in accordance with a study in Saudi Arabia which shows that women are twice as likely to get UTIs as men in all age groups.[13] UTIs are commonly associated with the anatomical structure of the lower urinary tract in women. The female external urethra is adjacent to the vagina and gastrointestinal tract, therefore, normal intestinal flora can more easily migrate to the vagina and then to the urinary tract and become pathogenic.[14,15] In addition, the female urethra is also shorter than the male's.

The high incidence of fungal UTIs in the older population is associated with decreased function of the immune system or immunosenescence, more frequent exposure to nosocomial pathogens, and the emergence of comorbidities that can increase the risk of UTIs, such as the use of urinary catheters and decreased cognitive function.[15] In postmenopausal women, risk factors for UTIs increase due to changes in the urogenital epithelium resulting from estrogen levels. These changes result in changes in the composition of the normal urethral flora, increase in pH, and cause the urinary tract to become more hospitable for the growth of pathogens.[16]

In this study, there were various comorbid diseases, especially in the non-DM group. The most common comorbidity was hypertension. Although neither hypertension nor antihypertensive medications have a direct relationship with UTIs, hypertension is a major risk factor for many other diseases such as chronic kidney disease (CKD) which can lead to a chronic inflammation state, weaken the body's immune response, and eventually increases risk of UTIs.[17,18] Another common comorbidity is dyslipidemia, which can be a risk factor for atherosclerotic cardiovascular diseases such as coronary artery disease, peripheral artery disease, or cerebrovascular accident; all of which can cause disability and increase the risk of UTIs.[19] Moreover, patients with malignancy have a suppressed immune response due to cancer progression and the side effects of chemotherapy.[20,21] Patients with autoimmune disease such as systemic lupus erythematosus (SLE) become susceptible to infection through several mechanisms, for example, intrinsic immunological abnormalities induced by the disease and immunosuppressive treatments given to patients.[22] Meanwhile, regardless the frequent co-infection with HIV/AIDS, tuberculosis (TB) is more prevalent among the economically poor society, in which they have limited access to adequate health care, nutrition, and habitation that will make them prone to infections like UTIs.[23]

Interestingly, the incidence of *C. albicans* resistance in DM patients was not significantly higher than non-DM patients, suggesting the possibility of failure of fungal infection therapy in DM patients due to changes in pharmacokinetics and pharmacodynamics and not due to internal changes in the pathogen. The main obstacle to antifungal therapy in DM patients is the bioavailability of drugs in plasma.[24]

The most common antifungal resistance in this study was found to be against micafungin, followed by caspofungin. Both of these antifungals belong to the class of echinocandins, which work by inhibiting the synthesis of 1,3-β-glucan that contribute to the fungal cell wall integrity.[25] The increasing number of resistance to micafungin may be related to the preferences of the majority of clinicians in the study sites as the main choice of systemic therapy for fungal infections due to its pharmacological properties. Echinocandins are considered superior to other antifungal groups, as they possess less toxicity than amphotericin B and fewer drug interactions than azoles. The relationship between clinician preference and increasing rates of drug resistance rates has been observed in India, in which the antifungal with the highest rate of resistance was the same as the clinicians' preferred antifungal, namely fluconazole.[26] The safety of antifungal agents is crucial because they are often used in patients with multiple underlying medical conditions and in the clinical care setting.[25] As a follow-up in the future, it is necessary to make guidelines for the use of antifungals in hospitals based on the pattern of resistance that exists in that hospital.

Candida spp. strains resistant to the echinocandins frequently show alteration in the glucan-producing enzyme complex that reduce their sensitivity to inhibitory activity. In these strains, point mutations are found in the fks1 or fks2 genes. These two genes encode the integral membrane proteins Fks1p and Fks2p, which are catalytic subunits of the glucan-synthesizing enzyme complex. Mutations in fks produces strains that are resistant to all members of the echinocandins group. This is thought to be the cause of the increasing number of caspofungin resistances along with micafungin resistance.[27, 28]

The limitation of this study is that UTI has not been classified based on the catheter use which may be associated with different causative organisms. Future studies are recommended to explore the relationship between DM and antifungal sensitivity in catheter-associated UTI patients. Moreover, the number of isolates from DM patients and non-DM patients was not the same, therefore it could not be compared statistically.

In conclusion, the prevalence of *Candida albicans* in DM and non-DM patients with UTIs is more than half. Female is more susceptible to experiencing UTIs. *Candida albicans* is resistant to micafungin in both DM and non-DM patients with UTIs, however, micafungin can still be considered appropriate as the first line empiric therapy in treating fungal UTIs.

As a follow-up in the future, it is necessary to make guidelines for the use of antifungals in hospitals based on resistance pattern in hospital. In addition, education about the importance of personal hygiene, especially for women, needs to be carried out, such as the correct technique for washing the perineal and the proper way to use underwear in order to prevent UTIs.

References

1. de Oliveira Santos GC, Vasconcelos CC, Lopes AJO, de Sousa Cartágenes MDS, Filho A, do Nascimento FRF, et al. Candida infections and therapeutic strategies: mechanisms of action for traditional and alternative agents. Front Microbiol. 2018;9:1351.
2. Kim SJ, Ryu JH, Kim YB, Yang SO. Management of Candida urinary tract infection in the elderly. Urogenit Tract Infect. 2019;14(2):33–41.
3. Mba IE, Nweze EI. Mechanism of Candida pathogenesis: revisiting the vital drivers. Eur J Clin Microbiol Infect Dis. 2020;39(10):1797–819.
4. Harreiter J, Roden M. [Diabetes mellitus-definition, classification, diagnosis, screening and prevention (Update 2019)]. Wien Klin Wochenschr. 2019;131(Suppl 1):6–15.
5. Kumar A, Gangwar R, Zargar AA, Kumar R, Sharma A. Prevalence of diabetes in India: a review of IDF Diabetes Atlas 10th Ed. Curr Diabetes Rev. 2024;20(1):e130423215752.
6. Dostalek M, Akhlaghi F, Puzanovova M. Effect of diabetes mellitus on pharmacokinetic and pharmacodynamic properties of drugs. Clin Pharmacokinet. 2012;51(8):481–99.
7. Duffus J, Templeton DM, Schwenk M. Comprehensive glossary of terms used in toxicology. Chemistry Int. 2018;40(3):38–9.

8. Mohd Sazlly Lim S, Sinnollareddy M, Sime FB. Challenges in antifungal therapy in diabetes mellitus. J Clin Med. 2020;9(9):2878.
9. Szkudlarek A, Sułkowska A, Maciążek-Jurczyk M, Chudzik M, Równicka-Zubik J. Effects of non-enzymatic glycation in human serum albumin. Spectroscopic analysis. Spectrochim Acta A Mol Biomol Spectrosc. 2016;152:645–53.
10. Lonardo A, Lugari S, Ballestri S, Nascimbeni F, Baldelli E, Maurantonio M. A round trip from nonalcoholic fatty liver disease to diabetes: molecular targets to the rescue? Acta Diabetol. 2019;56(4):385–96.
11. Rodrigues CF, Rodrigues ME, Henriques M. *Candida sp.* infections in patients with diabetes mellitus. J Clin Med. 2019;8(1):76.
12. Woldemariam HK, Geleta DA, Tulu KD, Aber NA, Legese MH, Fenta GM, et al. Common uropathogens and their antibiotic susceptibility pattern among diabetic patients. BMC Infect Dis. 2019;19(1):43.
13. Abou Heidar NF, Degheili JA, Yacoubian AA, Khauli RB. Management of urinary tract infection in women: a practical approach for everyday practice. Urol Ann. 2019;11(4):339–46.
14. Abelson B, Sun D, Que L, Nebel RA, Baker D, Popiel P, et al. Sex differences in lower urinary tract biology and physiology. Biol Sex Differ. 2018;9(1):45.
15. Rodriguez-Mañas L. Urinary tract infections in the elderly: a review of disease characteristics and current treatment options. Drugs Context. 2020;9:2020-4-13.
16. Jung C, Brubaker L. The etiology and management of recurrent urinary tract infections in postmenopausal women. Climacteric. 2019;22(3):242–9.
17. Gremke N, Kostev K, Kalder M. Association between antihypertensive medication and the risk of urinary tract infection (UTI) of outpatients: a retrospective cohort study. Infection. 2023;51(2):417–24.
18. Shankar M, Narasimhappa S, Madhura NS. Urinary tract infection in chronic kidney disease population: a clinical observational study. Cureus. 2021;13(1):e12486.
19. Ray KK, Ference BA, Séverin T, Blom D, Nicholls SJ, Shiba MH, et al. World Heart Federation Cholesterol Roadmap 2022. Glob Heart. 2022;17(1):75.
20. Audi ZF, Saker Z, Rizk M, Harati H, Fares Y, Bahmad HF, et al. Immunosuppression in medulloblastoma: insights into cancer immunity and immunotherapy. Curr Treat Options Oncol. 2021;22(9):83.
21. Ballow M, Sánchez-Ramón S, Walter JE. Secondary immune deficiency and primary immune deficiency crossovers: hematological malignancies and autoimmune diseases. Front Immunol. 2022;13:928062.
22. Sawada T, Fujimori D, Yamamoto Y. Systemic lupus erythematosus and immunodeficiency. Immunol Med. 2019;42(1):1–9.
23. Pathak D, Vasishtha G, Mohanty SK. Association of multidimensional poverty and tuberculosis in India. BMC Public Health. 2021;21(1):2065.
24. Aitken-Saavedra J, Lund RG, González J, Huenchunao R, Perez-Vallespir I, Morales-Bozo I, et al. Diversity, frequency and antifungal resistance of Candida species in patients with type 2 diabetes mellitus. Acta Odontol Scand. 2018;76(8):580–6.
25. Szymański M, Chmielewska S, Czyżewska U, Malinowska M, Tylicki A. Echinocandins - structure, mechanism of action and use in antifungal therapy. J Enzyme Inhib Med Chem. 2022;37(1):876–94.
26. Arun CS, Raju P, Lakshmanan V, Kumar A, Bal A, Kumar H. Emergence of fluconazole-resistant candida infections in diabetic foot ulcers: implications for public health. Indian J Community Med. 2019;44(Suppl 1):S74–6.
27. Lee Y, Puumala E, Robbins N, Cowen LE. Antifungal drug resistance: molecular mechanisms in *Candida albicans* and beyond. Chem Rev. 2021;121(6):3390–411.
28. Sakagami T, Kawano T, Yamashita K, Yamada E, Fujino N, Kaeriyama M, et al. Antifungal susceptibility trend and analysis of resistance mechanism for Candida species isolated from bloodstream at a Japanese university hospital. J Infect Chemother. 2019;25(1):34–40.