Antifungals Patterns in Critical Patients with Candidiasis in the Intensive Care Units at Sanglah General Hospital 2019

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Abstract

Introduction: The prompt initiation of appropriate antifungal therapy is essential in controlling invasive candidiasis and improving the prognosis in critical patients undergoing treatment in the Intensive Care Unit. Candida Score (CS) can assess patients at risk of candidiasis and is expected to assist clinicians in starting antifungal therapy in patients suspected Candidiasis. The purpose of this study was to determine the pattern of antifungal administration in critically ill patients with candidiasis in the Intensive Care Unit at Sanglah General Hospital.

Methods: The design of this study is a cross-sectional descriptive study involving critically ill patients who were under treatment in the Intensive Care Unit of Sanglah General Hospital from January to June 2019. The patients included in this study were patients who were ≥ 18 years old and under treatment in ICU for at least seven days.

Results: There are 64 patients undergoing treatment in the Intensive Care Unit. From 64 patients, 6 pasien had CS = 0, 29 patients had CS = 1, 13 patients had CS = 2, 11 patients had CS = 3, 5 patients had CS = 4, and no patients had CS = 5. Eleven patients received empirical antifungal therapy. All empirical antifungal therapies use the Triazole group.

Conclusion: We found that 11 of 16 patients with a CS value of ≥ 2.5 were given empirical antifungal therapy, while 48 patients with a CS value of < 2.5 were not given empirical antifungal therapy.

Keywords: *Invasive Candidiasis, Candida Score, Empirical Antifungal Therapy.*

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Introduction

Candida species are one of the most common pathogens that infect patients in hospitals, especially in the Intensive Care Unit (ICU).¹ Candidiasis is causing significant mortality and morbidity.² The incidence of candidiasis is quite high in the Intensive Care Unit. It has been reported that Candida ranks third as the most frequently infecting species in ICU, and about 843 (17%) of the 4947 patients treated at ICU were infected with Candida species.³ Candidiasis often causes death in patients in the hospital, especially in ICU. Mortality rates related to candidiasis can reach 40 - 70% in ICU.⁴⁻⁶

This high mortality rate is caused by the difficulty of establishing an early diagnosis. Immediate initiation of suitable antifungal therapy is essential for controlling candidiasis, and this has been shown to reduce mortality.⁷ Guidelines are needed in providing appropriate antifungal therapy and to avoid the use of unnecessary antifungal therapy.

Candida Score (CS) can assess patients who are at risk of infection with candidiasis and, in their assessment use four risk factors, namely: multifocal Candida colonization, severe septic

/ septic shock, surgery, and total parenteral nutrition.⁸ This Candida Score is expected to help clinicians to start antifungal therapy so there is no excessive use of antifungal therapy associated with increased health costs and the development of resistance from Candida, and the lack of use of antifungal therapy associated with worsening prognosis in critically ill patients.⁸⁻¹⁰

Methods

This study is a cross-sectional descriptive study involving critically ill patients who were under treatment in the Intensive Care Unit of Sanglah General Hospital, Denpasar-Bali, Indonesia, from January to June 2019. The sample collection technique used in this study is a total sampling. The patients included in this study were patients who were ≥ 18 years old and under treatment in ICU for at least seven days. Exclusion criteria were as follows: neutropenia defined as a total leukocyte count $< 500/\text{mm}^3$, mothers who are breastfeeding or pregnant women, patients who infected with Candida species or currently on antifungal therapy for the first seven days in ICU. This study protocol was approved by the Committee of Ethical Research of Udayana University/Sanglah General Hospital. The data that have been collected and categorized are analyzed using IBM SPSS Statistics version 23 software.

Results

Sixty-four patients were included in this study. The most common age group was 60 – 69 years and the male-to-female ratio was 1.37:1. Patient characteristics such as age, gender, diagnosis on ICU admission, Apache II Score and ICU length of stay are shown in Table 1.

Table 1. Characteristic of the patients

Characteristics	N = 64
Age (%)	
< 20 Years	4 (6.25)
20 - 29 Years	6 (9.38)
30 - 39 Years	4 (6.25)
40 - 49 Years	12 (18.75)
50 - 59 Years	12 (18.75)
60 - 69 Years	16 (25)
70 - 79 Years	9 (14.06)
≥ 80 Years	1 (1.56)
Gender (%)	
Male	37 (57.8)
Female	27 (42.2)
Diagnosis of ICU admission (%)	
Surgical	39 (60.9)
Non-Surgical	25 (39.1)
Apache II Score	
≥ 15	44 (68.8)
< 15	20 (31.2)
ICU Length of stay	
Median (Min-Max)	11.5 (7-48) days

Table 2. Distribution variable of Candida Score

Variable of Candida Score	Value of Candida Score				
	1 (n = 29)	2 (n = 13)	3 (n = 11)	4 (n = 5)	5 (n = 0)
Total parenteral Nutrition	4	11	3	5	0
Severe Sepsis / Septic Shock	0	2	11	5	0
Multifocal Candida Colonization	0	0	1	1	0
Surgery	25	11	7	4	0

In this study we found the distribution of Candida Score values as follows: 6 patients had CS = 0; 29 patients had CS = 1; 13 patients had CS = 2; 11 patients had CS = 3; 5 patients had CS = 4; and no patient had CS = 5. Table 2 shown the distribution variable of Candida Score. The distribution as follows: 47 (73.4%) patients were postoperative patients; 23 (35.9%) patients used total parenteral nutrition; 18 (28.1%) patients had severe sepsis / septic shock; and 2 (3.1%) patients had multifocal Candida colonization

Table 3. Value of Candida Score according to the empirical antifungals treatments

Value of Candida Score	Initiation of Empirical Antifungal Therapy		Total
	Given (Triazole)	Not Given	
0	0	6	6
1	0	29	29
2	0	13	13
3	8	3	11
4	3	2	5
5	0	0	0

From this study, we found that empirical antifungal therapy was initiated in 11 of 16 (68.7%) patients with Candida Score ≥ 2.5 and no empirical antifungal therapy was initiated in 48 patients with CS < 2.5 . All empirical antifungal therapies used the Triazole group.

Thirty-six (56%) patients died during their ICU stay. Among the 11 patients who were given empirical antifungal therapy, 9 (81.8%) died, whereas among 53 patients who were not given antifungal therapy, 27(50.9%) died.

Table 4. Outcome of the patient according to the initiation of empirical antifungal therapy

Initiation of Empirical Antifungal Therapy	Outcome		Total
	Alive	Dead	
Given (Triazole)	2	9	11
Not Given	26	27	53

Discussion

Candida Score is a simple scoring system that may help clinicians in differentiating between invasive Candidiasis and Candida species colonization in non-neutropenic critically ill patients.^{8,9} Candida Score can also be used as a reference in starting empirical antifungal therapy.⁹ Candida Score had a sensitivity of 81% and a specificity of 74% with a cut-off value of 2.5.⁸

In this study, 16 (25%) patients had a CS value > 2.5 and 48 (75%) patients had a CS value < 2.5 . Similar results are also founded in the study conducted by León *et al.* León *et al.*,⁹ reported that there were 327 (36.65%) patients who had a Candida Score ≥ 3 . However, different results were reported by Leroy *et al.* Leroy *et al.*,¹⁰ reported that patients with a Candida Score ≥ 3 had the highest percentage of 53.19%. The difference in these results can occur because one of the inclusion criteria in a study conducted by Leroy *et al.* was severe septic or septic shock so that the patients in the study had a minimum value of Candida Score is two.¹⁰

Empirical antifungal therapy was only given to 11 (68.8%) of 16 patients who had a Candida Score ≥ 2.5 , whereas empirical antifungal therapy was not given to all patients with a Candida Score < 2.5 . These results are different from the previous study conducted by Leroy *et al.* Leroy *et al.*,¹⁰ found that 18 (36%) of 50 patients with CS values ≥ 2.5 and 1 (2.3%) of 44 patients with CS values < 2.5 received empirical antifungal therapy. This difference in results can be caused by the decision of the doctor in charge of the patient. The use of the antifungal agent for the treatment of candidiasis should take into account the history of intolerance to an antifungal agent, the dominant Candida species and current susceptibility data in a particular clinical unit, the severity of illness, relevant comorbidities, and evidence of involvement of the CNS, cardiac valves or visceral organs.¹¹ The doctor must also consider the risks of toxicity, cost-effectiveness, the patient's willingness to be given antifungal therapy, and whether the patient is pregnant or not.¹¹

Leroy *et al.*,¹⁰ in their study, found that 10 (53%) of 19 patients given empirical antifungal therapy died and 36 (48%) of 75 patients who were not given antifungals died during their ICU stay. They also found that mortality in patients who had CS > 3 and received empirical antifungal therapy was no different from patients who had CS > 3 and did not receive empirical antifungal therapy (6/10 vs. 7/11; $p = 1$). In this study, empirical antifungal therapy was given to 11 patients and 9 (80.8%) of them died, whereas empirical antifungal therapy was not given to 53 patients and 27 (50.8%) of them died.

The risk of mortality among patients with candidiasis related to increasing age, higher APACHE II scores, infecting Candida species, immunosuppressive agents, and antifungal selection.¹¹ In this study, the characteristics of patients with the age group 60-69 years had the highest percentage of 25%. Besides, patients with Apache II Score ≥ 15 also had the highest percentage of 68.8%. In our opinion, these two characteristics of our subject might have contributed to the high mortality rate in this study. Also, the use of the Triazole group as

empirical antifungal therapy can increase the risk of death in this study. Based on Infectious Diseases Society of America guideline, preference should be given to an echinocandin in hemodynamically unstable patients, in those colonized with Azole-resistant Candida species and those previously exposed to an Azole antifungal group. Fluconazole may be considered in hemodynamically stable patients who have no prior exposure to Azoles antifungal group or who are colonized with Azole-susceptible Candida species. The Echinocandins group demonstrates significant fungicidal activity against most Candida species, and each of these agents has demonstrated success in approximately 70-75% of patients.¹¹ The Echinocandins group has exceptional efficacy, limited drug interactions, a good safety profile, and concerns about fluconazole resistance, leading many experts to choose echinocandins as initial therapy for most adult patients with candidiasis.¹¹ Only one study comparing an Echinocandin group to Fluconazole has been performed, and the results from this study was Anidulafungin suggest a strong trend toward more favorable outcomes compared with Fluconazole as primary therapy for candidiasis.¹² A combined analysis of 7 of the largest randomized clinical trials comparing treatment for candidemia and invasive candidiasis and involving almost 2000 patients found that initial therapy with an Echinocandin was a significant predictor of survival.¹³ However, this is still the author's opinion so that further research needs to be done related to resistance and susceptible patterns of antifungal agent in the ICU Sanglah General Hospital, Denpasar, Bali, Indonesia.

This study has limitations such as the lack of samples used in this study when compared to the number of samples conducted by Leroy *et al.*¹⁰ and León *et al.*⁹. The small number of samples was because this study was only conducted at one tertiary type hospital in Bali, and data were also taken from patients undergoing treatment in the Intensive care Unit from January to June 2019. In addition, prospective research is needed to find out reasons why doctors do not give empirical antifungal therapy to patients who have a Candida Score > 2.5 and the incidence rate of candidiasis in the ICU Sanglah General Hospital.

Conclusion

The pattern of antifungal administration in critically ill patients with candidiasis in Sanglah General Hospital has relevance to Candida Score. In this study was found that 11 of 16 patients with a CS value > 2.5 were given empirical antifungal therapy, while 48 patients with a CS value of < 2.5 were not given empirical antifungal therapy.

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The authors report no conflict of interest.

References

1. Guo F, Yang Y, Kang Y, *et al.* Invasive candidiasis in intensive care units in China: a multicentre prospective observational study. *J Antimicrob Chemother.* 2013;68:1660–1668. DOI:10.1093/jac/dkt083

2. Guzman JA, Tchokonte R, Sobel JD. Septic Shock Due to Candidemia: Outcomes and Predictors of Shock Development. *J Clin Med Res*. 2011;3(2):65–71. DOI:10.4021/jocmr536w
3. Vincent J, Rello J, Marshall J, et al. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. *JAMA*. 2009;302(21):2323–2329. DOI:10.1001/jama.2009.1754.
4. Lortholary O, Renaut C, Sitbon K, et al. Worrisome trends in incidence and mortality of candidemia in intensive care units. *Intensive Care Med*. 2014;40:1303–1312. DOI:10.1007/s00134-014-3408-3
5. Kett DH, Azoulay E, Echeverria PM, et al. Candida bloodstream infections in intensive care units: Analysis of the extended prevalence of infection in intensive care unit study*. *Crit Care Med*. 2011;39(4):665–670. DOI:10.1097/CCM.0b013e318206c1ca
6. Bassetti M, Ansaldi F, Diaz-martin A, et al. A multicenter study of septic shock due to candidemia: outcomes and predictors of mortality. *Intensive Care Med*. 2014;40:839–845. DOI:10.1007/s00134-014-3310-z
7. Parkins MD, Sabuda DM, Elsayed S, et al. Adequacy of empirical antifungal therapy and effect on outcome among patients with invasive Candida species infections. *J Antimicrob Chemother*. 2007;60:613–618. DOI:10.1093/jac/dkm212
8. León C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system (“Candida score”) for early antifungal treatment in nonneutropenic critically ill patients with Candida colonization. *Crit Care Med*. 2006;34(3):730–737. DOI:10.1097/01.CCM.0000202208.37364.7D
9. León C, Ruiz-santana S, Saavedra P, et al. Usefulness of the “Candida score” for discriminating between Candida colonization and invasive candidiasis in non-neutropenic critically ill patients: A prospective multicenter study. *Crit Care Med*. 2009;37(5):1624–1633. DOI:10.1097/CCM.0b013e31819daa14
10. Leroy G, Lambiotte F, Thévenin D, et al. Evaluation of “Candida score” in critically ill patients : a prospective , multicenter , observational , cohort study. *Ann Intensive Care*. 2011;1(1):50. DOI:10.1186/2110-5820-1-50.
11. Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62(4):1–50. DOI:10.1093/cid/civ933
12. Andes DR, Safdar N, Baddley JW, et al. Impact of Treatment Strategy on Outcomes in Patients with Candidemia and Other Forms of Invasive Candidiasis: A Patient-Level Quantitative Review of Randomized Trials. *Clin Infect Dis*. 2012;54(8):1110–1122. DOI:10.1093/cid/cis021
13. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus Fluconazole for Invasive Candidiasis. *N Engl J Med*. 2007;356(24):2472–2482. DOI:10.1056/NEJMoa066906

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