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Evaluation of the effect of antibiotics used during parenteral nutrition treatment on Candidemia

Nadir Yalçın[1]*, Nursel Sürmelioğlu[2], Özlem Özkan-Kuşcu[3], Burcu Kelleci-Çakır[1], Kutay Demirkan[1], Murat Gündüz[4]

SUMMARY

OBJECTIVE: Parenteral nutrition is an important risk factor for candidemia. In this risk analysis study, the effect of previous antibiotic administration apart from the length of hospital stay, duration of Parenteral nutrition treatment, and *Candida* score parameters on developing candidemia was evaluated in the non-neutropenic patients receiving Parenteral nutrition treatment.

METHODS: In this double center, retrospective, and cross-sectional study, the data of patients who received Parenteral nutrition treatment were collected. Patients with or without candidemia after the initiation of Parenteral nutrition treatment were compared in terms of demographic features, *Candida* score, length of hospital stay, duration of Parenteral nutrition treatment, and previous use of antibiotics. Then, predictor factors affecting the probability of candidemia during *Candida* growth time were determined by the Cox regression analysis.

RESULTS: A total of 148 patients (59.5% males) were included and 16 (10.81%) of these had candidemia after initiation of parenteral nutrition treatment. The median (min–max) duration of parenteral nutrition treatment was 11 (4–72) days and the *Candida* growth time was 13 (7–29) days. Statistically significant differences were found between patients with or without candidemia groups in terms of length of hospital stay ($p<0.001$), duration of parenteral nutrition treatment ($p<0.001$), and *Candida* score ($p<0.001$). To determine the effect of these variables and antibiotics on candidemia, length of hospital stay [Hazard Ratio 1.030; $p=0.021$] and piperacillin–tazobactam (Hazard Ratio 5.626; $p=0.030$) were found significant and independent risk factors on the development of candidemia.

CONCLUSION: There are some well-known risk factors including length of hospital stay, duration of Parenteral nutrition treatment, and *Candida* score; the potential impact of piperacillin–tazobactam administration should also be considered since they may be effective on the development of candidemia.

KEYWORDS: Parenteral nutrition. Candidemia. Risk factors. Antibiotic. Piperacillin-Tazobactam.

INTRODUCTION

Hospital-acquired *Candida* and bloodstream infections (BSI) represent approximately 9% of all nosocomial BSI[1]. In a multi-centered, point prevalence study conducted on the sepsis cases with causative agents in the intensive care unit (ICU), the rate of *Candida* was determined to be 4.7%[2]. While the candidemia-related mortality rate was 83%, invasive candidiasis was found to be an independent risk factor for mortality[3]. Parenteral nutrition (PN) is consistently identified as an independent risk factor for candidemia in both neutropenic and non-neutropenic patients. The mortality rate of *Candida* catheter-related BSI in patients on PN treatment was found 30%[4]. Potential mechanisms that may be responsible for the increase in the candidemia risk include intestinal mucosal atrophy and subsequent translocation of microorganisms

[1]Hacettepe University, Faculty of Pharmacy, Department of Clinical Pharmacy – Ankara, Turkey.
[2]Çukurova University, Faculty of Pharmacy, Department of Clinical Pharmacy – Adana, Turkey.
[3]Adana Seyhan State Hospital, Department of Intensive Care Unit – Adana, Turkey.
[4]Çukurova University, Faculty of Medicine, Department of Anesthesiology and Reanimation – Adana, Turkey.
*Corresponding author: nadir.yalcin@hotmail.com
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or endotoxins, hyperglycemia, nutrient-rich components supporting bacterial and fungal growth, and indwelling parenteral access devices[5]. According to a retrospective, case–control study, both hospital and ICU length of hospital stay (LOS) are time-dependent risk factors for candidemia (p<0.001)[6]. PN exposure time is a risk factor for the development of candidemia, especially in critically ill patients. According to Chow et al., PN duration was a significant risk factor for the development of candidemia in all patients with or without *Candida albicans* (p<0.01)[4]. PN is lifesaving when it is needed but besides the benefit of PN, determining the risk of developing candidemia in patients and initiation of the most appropriate antifungal treatment at the most propitious time can minimize the occurrence of PN-related candidemia[5]. PN treatment indications, safe administration techniques, and duration are reported in both the American Society for Parenteral and Enteral Nutrition (ASPEN) and European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines[7,8]. León et al. developed a bedside "*Candida* score" to decide early antifungal treatment in non-neutropenic critically ill patients with *Candida* colonization. The "Candida score" for a cutoff value of 2.5 points were as follows for deciding early antifungal treatment: PN, surgery, multifocal colonization (1 one point each), and severe sepsis (2 two points)[9].

In this risk analysis study, the effect of antibiotic administration apart from LOS, duration of PN treatment, and *Candida* score (i.e., clinical sepsis, PN administration, surgery, and multifocal colonization) parameters on developing candidemia was evaluated in the non-neutropenic patients receiving PN treatment.

METHODS

Patients

In this double-center, retrospective, and cross-sectional study, the data of patients who received PN treatment between January 2019 and December 2019 were collected. Patients aged 18 years or older, who were non-neutropenic (neutropenia: neutrophil count $<0.1\times10^9$ cells/L) and did not receive chemotherapy during PN treatment, who had available culture test results, and who did not have candidemia before PN treatment were included. PN treatment was evaluated by the clinical nutrition team, and only the patients who indicated PN treatment were able to receive the PN treatment. Multi-chamber bag PN was administered to all patients in this study (OliClinomel® N4-550E; Baxter Healthcare Corporation). The patients with and without candidemia after PN were compared in terms of demographic features (i.e., age, gender, and admitted department), LOS, duration of PN treatment, leukocyte and platelet counts, and concomitantly administration of antibiotics.

The time from the start of PN treatment until the development of candidemia was determined as the *Candida* growth time. According to blood culture tests, *Candida* species was reported as *C. albicans* for all study patients by the microbiology laboratory. The patients who were prescribed antibiotics before PN treatment were excluded from this study. Patients who were prescribed at least one antibiotic and only their antibiotic treatments that have been initiated after the initiation of PN treatment and before the development of candidemia were included in this study. The duration of antibiotic treatment is at least 7 days for all study patients. Also, the patients who received fluconazole prophylaxis before the development of candidemia were excluded from this study. This study protocol was approved by the Çukurova University Ethics Committee (Decision No. 2020/56-105).

Statistical analysis

Chi-square test, Fisher's exact test, Student's *t*-test, Mann–Whitney U test, Poisson regression, and Cox regression analysis, whichever appropriate, were performed. Our collective data met the criteria of a Cox distribution (multivariate model), and the appropriate model had been adjusted to determine the independent predictors of the patient outcome. According to the literature and clinical experience, we created two different models, namely, a model with *Candida* score, LOS, and duration of PN treatment and another model with narrow and broad-spectrum antibiotics administered during PN treatment. For all tests, p<0.05 was considered statistically significant. According to the Omnibus test in Cox regression analysis, having all the independent variables in our example models, we have p-values for first (–2 Log-Likelihood: 51.84; p=0.025) and second models (-2 Log-Likelihood: 38.80; p=0.017), indicating statistically significant overall model. IBM SPSS Statistics 23.0 software was used to analyze and evaluate the data. Since the medical literature does not contain similar studies, the sample size could not be calculated. However, at the end of this study, the power analysis result was determined as 98.06% (G*Power 3.1 Statistical Power Analysis).

RESULTS

Patients' characteristics

A total of 148 patients [88 (59.5%) males] with the mean (standard deviation, SD) age of 63.92±18.85 years were included. Half of the patients were admitted in ICU (50.0%) wards. The median (min–max) LOS was 22 days (5–206 days). The most commonly prescribed antibiotics in these patients were cephalosporins (n=60) (Table 1).

Table 1. Distribution of demographic characteristics and antibiotic treatments of the study population (n=148).

Gender, male, n (%)	88 (59.5)
Age, mean±SD	63.92±18.85
Leukocyte, median (min–max)	10170 (1300–37000)
Platelet, median (min–max)	242000 (18000–821000)
Number of patients in ICU, n (%)	74 (50.0)
LOS, median (min–max) days	22 (5–206)
Duration of PN treatment, median (min–max) days	11 (4–72)
Candida growth time, median (min–max) days	13 (7–29)
Candida score, median (min–max)	2 (1–5)
Candidemia, n (%)	16 (10.8)
Use of antibiotics (narrow spectrum), n (%)	71 (48.0)
Use of antibiotics (broad spectrum), n (%)	131 (88.5)
Antibiotic combinations (2 or more), n (%)	91 (61.5)
Carbapenems	59 (39.9)
Tigecycline	27 (18.2)
Piperacillin–tazobactam	22 (14.9)
Fluoroquinolones	15 (10.1)
Macrolides	5 (3.4)
Cephalosporins	50 (40.3)
Cefazolin	12 (8.1)
Glycopeptides	20 (13.5)
Aminoglycosides	15 (10.1)
Metronidazole	29 (19.6)
Colistin	8 (5.4)

SD: standard deviation; ICU: intensive care unit; LOS: length of hospital stay; PN: parenteral nutrition.

It was found that 16 (10.81%) patients had candidemia diagnosis after the initiation of PN treatment. In these patients, the median (min–max) duration of PN treatment was 11 (4–72) days, and the median (min–max) duration of *Candida* growth time after the initiation of PN treatment was 13 (7–29) days. In addition, antibiotic polypharmacy (2 or more) was determined in 91 (61.5%) patients (Table 2).

Correlation and regression analyses

Statistically significant differences were found between the with and without candidemia groups in terms of LOS ($p<0.001$), duration of PN treatment ($p<0.001$), and *Candida* score ($p<0.001$) (Table 2). Thirty (20.3%) patients were identified as high risk (≥3 points) according to the *Candida* score. There was a significant relationship between the patients with high risk according to the *Candida* score and the candidemia diagnosis ($p<0.001$). In addition, according to the Poisson regression analysis, the *Candida* score was a significant and independent predictor of the candidemia diagnosis ($p<0.001$). For every extra one point in *Candida* score, 1.169 (95%CI 1.110–1.231) times more candidemia was diagnosed (16.9% higher risk). However, the cutoff value (high risk as three or more points) for *Candida* score was not a significant predictor of the candidemia diagnosis ($p=0.224$).

A Cox regression was run to predict whether a patient treating with PN has a diagnosis of candidemia based on the *Candida* score, LOS, duration of PN treatment, narrow and broad-spectrum antibiotics (i.e.., carbapenems, tigecycline, piperacillin–tazobactam, cephalosporins, glycopeptides, and colistin) prescribed after the initiation of PN treatment. Since the number of patients who were prescribed fluoroquinolones, macrolides, cefazolin, aminoglycosides, and metronidazole in the candidemia (+) group was <2, these drugs were not included in the Cox regression analysis to ensure the validity of our model (Table 2). For every extra day in LOS, 1.030 (95%CI 1.004–1.057) times more candidemia risk was determined ($p=0.021$). Also, the hazard ratio (HR) for piperacillin–tazobactam (HR=5.626) indicates that patients who prescribed piperacillin–tazobactam treatment had a higher risk of candidemia than patients who do not ($p=0.030$). In contrast, the duration of PN treatment, *Candida* score, and other antibiotic treatments were not significant risk factors ($p>0.05$) (Table 3).

DISCUSSION

Candidemia was found in 10.81% of the patients who received PN in this study, which appears higher than the findings of (2–6%) other studies in the literature[10,11]. However, since all the patients who received PN treatment in the hospital were not included, our result is not reflecting the actual incidence due to the design of this study. There were significant differences between groups with and without candidemia in terms of LOS, duration of PN treatment, and *Candida* score. According to the Cox regression analysis, LOS and piperacillin–tazobactam (broad-spectrum antibiotic)

Table 2. Distribution of demographic characteristics and antibiotic treatments by candidemia.

	Candidemia (+) group (n=16)	Candidemia (-) group (n=132)	p-value
Gender, male, n (%)	9 (56.2)	79 (59.8)	0.78
Age, mean±SD	62.94±13.92	64.04±19.40	0.53
Leukocyte, median (min–max)	10170 (4800–17100)	10150 (1300–37000)	0.42
Platelet, median (min–max)	247500 (113000–821000)	241000 (18000–734000)	0.62
LOS, median (min–max) days	52 (17–206)	21 (5–127)	<0.001*
Duration of PN treatment,median (min–max) days	21 (9–69)	10.5 (4–72)	<0.001*
Candida growth time,median (min–max) days	13 (7–29)	0	–
Candida score, median (min–max)	3 (1–5)	2 (1–4)	<0.001*
Use of antibiotics(narrow spectrum), n (%)	8 (50.0)	66 (51.5)	0.24
Use of antibiotics(broad spectrum), n (%)	16 (100)	120 (90.9)	0.21
Antibiotic combinations(2 or more), n (%)	9 (56.3)	82 (62.1)	0.85
Carbapenems	9 (56.2)	50 (37.8)	0.16
Tigecycline	5 (31.2)	22 (16.6)	0.15
Piperacillin–tazobactam	4 (25.0)	18 (13.6)	0.22
Fluoroquinolones	0 (0)	15 (11.3)	0.15
Macrolides	1 (6.2)	4 (3.0)	0.54
Cephalosporins	4 (25.0)	56 (42.4)	0.16
Cefazolin	0 (0)	12 (9.0)	0.09
Glycopeptides	3 (18.7)	17 (12.8)	0.53
Aminoglycosides	0 (0)	15 (11.3)	0.32
Metronidazole	1 (6.2)	28 (21.2)	0.27
Colistin	2 (12.5)	6 (4.5)	0.45

*p<0.05. SD: standard deviation; LOS: length of hospital stay; PN: parenteral nutrition.

Table 3. Cox proportional hazard regression analysis.

	B	SE	Wald	Df	p-value	Hazard ratio(HR)	95%CI for HR
Length of hospital stay*	0.030	0.013	5.306	1	0.021	1.030	1.004–1.057
Duration of PN treatment	0.002	0.082	8.171	1	0.364	1.002	0.998–1.006
Candida score	-0.975	0.639	2.332	1	0.127	0.377	0.108–1.318
Carbapenems	1.214	0.902	1.812	1	0.178	3.366	0.575–9.706
Tigecycline	1.414	0.903	2.453	1	0.117	4.112	0.701–14.123
Piperacillin–tazobactam*	1.727	0.795	4.724	1	0.030	5.626	1.185–16.712
Cephalosporins	-0.180	1.264	0.020	1	0.887	0.835	0.070–9.941
Glycopeptides	1.775	1.034	2.946	1	0.086	5.902	0.777–14.800
Colistin	-0.186	1.013	0.034	1	0.854	0.830	0.114–6.043

Dependent variable: control group=0, study group = 1. Bold values indicate statistically significant variables. PN: parenteral nutrition; CI: confidence interval. *p<0.05.

administration were found to be independent risk factors for increased development of candidemia. However, the duration of PN treatment was not found to be a prediction risk factor in our model.

Although LOS and piperacillin–tazobactam administration were found as risk factors in this study, it is known that the factors affecting the development of candidemia may differ between patient groups depending on the chosen study design. Recent guidelines recommend the use of risk prediction tools to facilitate earlier recognition and initiation of antifungal treatment[12,13]. According to the study that used "*Candida* score," surgery, multifocal colonization, PN treatment, and severe sepsis were independent predictors of proven *Candida* infection[9]. In contrast, the sensitivity of this scoring system may differ in each patient group[13]. In this study, a significant relationship was found between *Candida* score and candidemia using the Poisson regression analysis. However, the cutoff points (high risk) for the score were not found as a significant predictor. This result means that the cutoff value of the *Candida* score should be reconsidered, especially in patients receiving PN treatment.

While broad-spectrum antibiotic was presented as a risk factor in some studies[10], the others were declared that the risk factor differs between the antibiotic groups[11,14]. In a case-control study, the previous use of antibiotics (OR 2.61; p=0.03) was found as an independent risk factor for the development of candidemia[15]. However, according to a case-comparator and 10-year study, piperacillin–tazobactam was not independently associated with BSI due to non-*C. albicans* species[14]. In contrast, in this study, the administration of piperacillin–tazobactam was determined as a significant and independent risk factor for the development of candidemia due to *C. albicans*. This result stated that the increasing use of broad-spectrum antibiotics, such as piperacillin–tazobactam, is an important risk factor especially for patients susceptible to candidemia due to PN treatment. Beyond our results, the influence of the presence of vancomycin and metronidazole with the risk of candidemia was reported[11].

According to a retrospective study, candidemia was developed after an average of 17.2 (5–74) days of administration of PN treatment. A similar result was determined in this study similar to 13 (7–29) days of the PN treatment[10]. Moreover, Luzzatti et al. reported that the elderly patients who received PN treatment had a significantly higher risk of candidemia even on the seventh day of PN treatment[11]. The fact that the mean age of our patient population (63.92 years) was close to the elderly people may explain the shorter *Candida* growth time in this study.

The LOS, duration of PN treatment, and *Candida* score were higher in patients with candidemia compared with patients without candidemia. Similar to our results, higher LOS and duration of PN treatment were also reported in patients who developed candidemia[11]. In another study whose primary outcome was the relationship between time-dependent risk factors and candidemia, LOS was greater in patients with candidemia versus control patients (36 days *versus* 13 days; p<0.001)[6]. In this study, with a similar result, statistically significant differences were found between the patients with and without candidemia groups in terms of LOS (52 days *versus* 21 days; p<0.001).

According to the study by Tsai et al., thrombocytopenia was associated with survival time in non-neutropenic patients requiring PN treatment after the onset of candidemia (p=0.006)[16]. In contrast, in this study, thrombocytopenia (<150000 cells/μL) was not determined, and it was not associated with the development of candidemia (p=0.62).

Particularly, since this is a retrospective study, it harbors some conspicuous limitations. Limited study period, small sample size, and lack of duration of antibiotic administration to evaluate the effect on the development of candidemia were the other limitations of this study.

CONCLUSIONS

This is the first study showing that piperacillin–tazobactam, a broad-spectrum antibiotic, is a significant and independent risk factor for candidemia in non-neutropenic patients receiving PN treatment. There are some well-known risk factors including the longer hospitalization and duration of PN treatment and higher *Candida* risk score; piperacillin–tazobactam treatment should also be considered as an important risk factor. Our data suggest that randomized controlled studies should be performed to evaluate the effectiveness of candidemia prevention by restricting the use of broad-spectrum antibiotics, such as piperacillin–tazobactam, and by managing PN treatment consistent with the current guidelines.

AUTHORS' CONTRIBUTIONS

NY: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **NS:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **OOK:** Data curation, Writing – original draft, Writing – review & editing. **BKC:** Investigation, Writing – original draft, Writing – review & editing. **KD:** Supervision, Visualization, Writing – review & editing. MG: Visualization, Writing – review & editing.

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