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**Risk factors and clinical analysis for PICC Related Fungal Colonization in
Premature Infants**

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Abstract

Objective: The present study aimed to analyze the risk factors for positive peripherally inserted central catheter (PICC) related fungal colonization in preterm infants.

Methods: A retrospective study was conducted in a tertiary hospital in southwest China between January 1, 2018 and December 31, 2020. The enrolled infants who underwent ultrasound-guided PICC insertion during hospitalization were born at < 32 weeks gestation or birth weight < 1500 grams. The demographics, the PICC related characteristics, the use of antibiotic, glucocorticoid and parenteral nutrition (PN) were collected from the medical record. Univariate and multivariate analyses were performed to investigate risk factors for PICC-related fungal colonization. Receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value by calculating the Yoden index.

Results: A total of 124 premature infants underwent ultrasound-guided PICC insertion. Among them, 19 patients had positive results of fungi at PICC tips. PN infusion duration (OR 1.37, 95%CI 1.05-1.79) and postnatal glucocorticoid exposure (OR 9.19, 95%CI 1.04-81.65) were independent risk factors for fungal colonization in PICC. The optimal cut-off value was 15 days, 28 days, respectively.

Conclusion: PICC tips fungal colonization is affected by postnatal glucocorticoid exposure and PN infusion duration. Appropriate clinical management should be adopted to avoid fungal colonization and fungemia.

Keywords: Peripherally inserted central catheter; Fungal Colonization; Premature Infants

Introduction

Peripherally inserted central catheters (PICCs) are widely used in neonatal intensive care units (NICUs), especially for the treatment of extremely preterm infants and very low birth weight (VLBW) infants to provide secure venous access or safe administration of hyperosmolar solutions^[1]. However, the use of PICCs increases the risk of catheter-related bloodstream infection (CRBSI), one of the most common nosocomial infections related to PICCs^[2, 3]. CRBSI was associated with several life-threatening complications, including necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), and retinopathy of prematurity (ROP), extended the hospital stay and the increased mortality or morbidity of premature infants^[1, 4]. It has been reported that bacteria were the most important pathogen of CRBSI^[5]. However, in premature infants, an increasing trend has been shown in fungal infections^[6], and the fungi were another common pathogen of CRBSI^[7, 8].

Fungal infection is a severe complication during PICC placement and is often fatal in very premature infants^[9]. The colonization of fungi in the catheters is the onset step of PICC-related fungal infections^[10, 11]. We also observed a high positive fungal culture from the PICC tips in our NICU over the past few years. Thus, in the present study, we aimed to explore the risk factors of PICC-related positive catheter tip cultures in very premature infants.

Results

1.General information

During the study period, 124 premature infants underwent ultrasound-guided PICC insertion. Among them, 31 patients were excluded because of the following reasons: 10 were obstructed, 1 had accidental detachment, 5 had catheter heterotopic, 6 had twice catheter inserted, 9 were excluded for deaths. The remaining 93 cases of catheter tips were cultured, of whom 28 patients were confirmed as having positive

cultures. The most commonly isolated microorganism was fungi (67.89%,19/28), Especially *Candida albicans* and *Candida glabrata*. The followed positive pathogen was bacteria (32.11%, 9/28) (Table 1). No patient had positive blood culture.

Table 1. Microorganisms cultured from catheter tip (n=28)

Microorganisms	2018	2019	2020	Total
Year				
Gram-positive bacteria				
<i>Streptococcus viridans</i>	1	-	-	1 (3.57%)
Gram-negative bacteria				
<i>Pseudomonas aeruginosa</i>	-	1	5	6 (21.43%)
<i>Morganella morganii</i>	-	-	1	1 (3.57%)
<i>Acinetobacter haemolyticus</i>	1	-	-	1 (3.57%)
Fungi				
<i>Candida albicans</i>	5	4	4	13 (46.43%)
<i>Candida glabrata</i>	2	2	2	6 (21.43%)

2.Univariate analysis of fungal colonization in PICC tips

We compared the medical parameters between positive and negative cases of fungal colonization at the catheter tip. As shown in Table 2, the positive group had a longer duration of PICC dwelling time ($P < 0.001$), antibiotic use ($P < 0.001$), postnatal glucocorticoid exposure ($P < 0.001$), and duration of PN ($P < 0.001$) than the negative group ,(Table 2).

Table 2. Univariate analysis of fungal colonization at the catheter tips

Parameters	Total(n=84)	Positive(n=19)	Negative (n=65)	$\chi^2/t/Z$	<i>P</i>
Demographics					
Gender (cases)				0.01	0.93
Male	45	10 (52.63%)	35 (53.85%)		
Female	39	9 (47.37%)	30 (46.15%)		
Gestational age (days)	206.5 (198, 220)	203 (193, 220)	207(199, 220)	1.18	0.24
Birth weight (grams)	1235±184	1270±192	1225±181	0.94	0.35

Mode of delivery (cases)					
Vaginal	60	15 (78.94%)	45 (69.23%)	0.68	0.41
Cesarean section	24	4 (21.05%)	20 (30.77%)		
Assisted reproductive technology (cases)				0.05	0.83
Yes	12	3(15.79%)	9(13.85%)		
No	72	16(84.21%)	56(86.15%)		
Twin (cases)				0.37	0.54
Yes	22	6(31.58%)	16(24.62%)		
No	62	13(68.42%)	49(75.38%)		
Premature rupture of membranes (cases)				2.39	0.12
Yes	20	2(10.53%)	18(27.69%)		
No	64	17(89.47%)	47(72.31%)		
PICC related characteristics					
Catheter insertion age (days)	4(2,6)	4(2,6)	4(2,6)	0.62	0.54
PICC dwelling time (days)	31 (24.25, 36)	37 (33, 44)	30 (23, 33)	4.23	<0.001
Treatment					
duration of antibiotic(days)	13.98±9.91	25.16±8.57	10.71±7.67	7.04	<0.001
Postnatal glucocorticoid exposure (cases)				18.29	<0.001
Yes	35	16 (84.21%)	19 (29.23%)		
No	49	3 (15.79%)	46 (70.77%)		
duration of PN (days)	28 (20,32.75)	35 (31,39)	25 (18.5,30)	5.29	<0.001

3. Multivariate logistic regression analysis for fungal colonization at PICC tips

Multivariate logistic regression was performed to identify the risk factors for fungal colonization . As shown in Table 3, all those factors increased the risk of fungal colonization. Logistic analyses demonstrated that with each additional day of antibiotic use and PN infusion, the risk of fungal colonization in PICC tips was increased by 9%, 28%, respectively. Postnatal exposure to the glucocorticoid also increased the risk by 9.19 times.

Table 3. Logistic regression analysis for fungal colonization at the catheter tips

Parameters	OR	95% CI	Adjusted OR	95% CI
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duration of antibiotic	1.23	1.11,1.35	1.09	0.98, 1.22
Postnatal glucocorticoid exposure	12.91	3.37, 49.51	9.19	1.04, 81.65
duration of PN	1.35	1.16,1.58	1.28	1.05, 1.56
PICC dwelling time	1.21	1.09,1.35	1.07	0.93,1.23

Duration of PN and PICC dwelling time were entered into the logistic regression model only one parameter at a time.

4. The optimal cut-off value for the duration of antibiotics and PN

The calculated optimal cut-off value for the duration of antibiotics and PN were 15days, 28days, respectively. Both the Area Under ROC Curve(AUC) were larger than 0.9, which showed a high diagnostic value (figure1). The Yoden index, sensitivity, and specificity are shown in table 4.

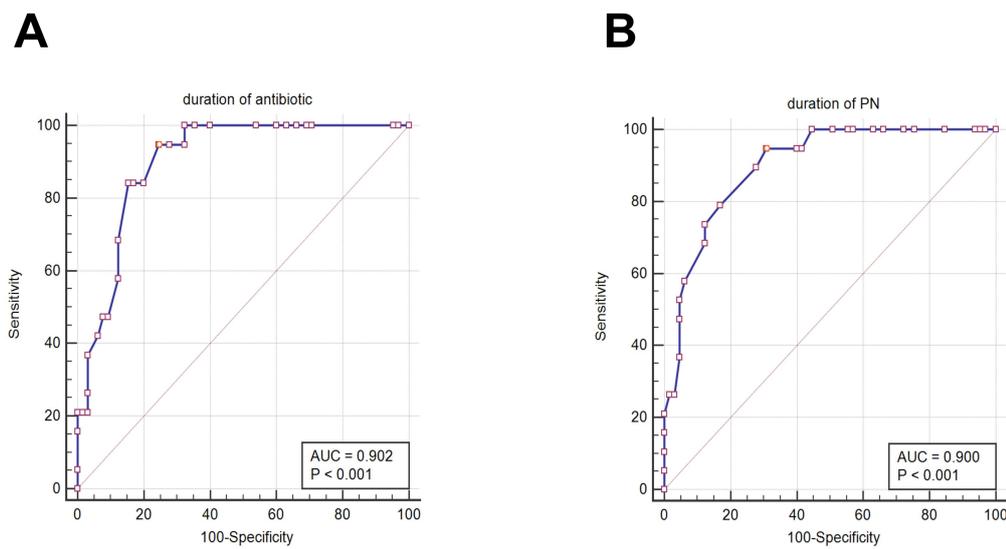


Figure 1. The ROC curve for the duration of antibiotic(A) and PN(B)

Table 4. The optimal cut-off value for the duration of antibiotic and PN

	duration of antibiotic	duration of PN
Youden index	0.70	0.64
Criterion(days)	>15	>28
Sensitivity	94.74	94.74
Specificity	75.38	69.23

Discussion

In recent decades, the incidence of premature infants has increased. Very premature infants or very low birth weight infants were undergone long hospitalization. Due to the poor peripheral vascular conditions, the use of PICC has increased significantly. However, exogenous catheters are associated with an increased risk of CRBSIs.^[12, 13] . Fungi-related CRBSIs are often fatal in very premature infants ^[9]. Therefore, it is indispensable to apply appropriate strategies for preventing fungi colonization in patients with PICCs.

Previous studies have shown that coagulase-negative staphylococcus was the predominant pathogen of CRBSIs in NICU ^[14, 15]. However, in recent years, it seems that the proportion of fungi was increased in PICC catheter-induced bloodstream infections ^[16]. In the present study, the positive rate of fungi colonization was higher than bacteria in PICC tips, and the main pathogen was *Candida albicans*. In our study, since early-onset sepsis incidence was high to 71.43%(60/84) among the included preterm cases, empiric broad-spectrum antibiotics were widely used. Therefore, the positive rate of bacteria in catheter tip culture is lower than the fungi. However, due to the small sample size, the duration of antibiotic use was not statistically significant. Despite this, the data still showed that the duration of antibiotics increased fungal colonization's clinical trend. The results indicated that the duration of antibiotics increased one day, the risk of fungal colonization in PICC tips was increased by 9%. The optimal cut-off value for the duration of PN was 15 days. Therefore, Risk assessment methods should be used to optimize early antibiotic practice^[17]. Antibiotics should be withdrawn as soon as possible without indication to reduce fungi colonization.

Glucocorticoid is widely used in very preterm infants to minimize the magnitude and duration of ventilatory support and decrease pulmonary morbidity. At the same time, it has been reported that glucocorticoids can increase the risk of fungal sepsis. Our study has similar results that postnatal glucocorticoid exposure increased the risk of catheter fungal colonization by 9.19 times. This might be related to dexamethasone therapy has side effects on neutrophils and lymphocytes, which enhanced the risk of fungal infection in preterm infants^[18]. Hence, strict guidelines should be implemented for the use of glucocorticoid in clinical practice. Patients should be monitored for fungal infections, especially those exposed to postnatal glucocorticoids.

After multivariate regression analysis, we determined that the duration of PN was a risk factor for fungal colonization in PICC tips. According to the literature^[19], PN's use appears to be a risk factor for the onset of CRBSI. It has been reported^[20-22] that PN can increase the risk of CRBSI by three to ten times. Our study demonstrated that the duration of PN increased one day, the risk of fungal colonization in PICC tips was increased by 28%. Fungi, especially *Candida* spp, which are notoriously adept at forming drug-resistant biofilm structures, are strongly adherent to surfaces and easily colonize in the PICC catheter. PN solutions contain electrolytes, micronutrients, and the macronutrients dextrose, amino acids, and lipid emulsions. Hypertonic glucose in the PN solutions is ideal for *Candida* growth, while fat emulsions are suitable for the growth of various microorganisms^[23]. These conditions increased the risk of fungal colonization or infections in PICC. The optimal cut-off value for the duration of PN was 28 days. In this study, PICC catheters were inserted once in all patients. This result suggests that long time use of PN infusion from the same PICC should be avoided. If it is needed, replacing PICC should be performed to reduce the risk of fungal colonization.

Previous studies have demonstrated that indwelling PICC is another independent risk factor for invasive fungal infections^[6, 10]. In our study, due to a strong relationship between PICC dwelling and PN use, they were entered into the multivariate logistic regression model, respectively. Although having statistical significance in the univariate model, for the small sample size, no statistical significance was observed in the adjusted OR of the duration of PICC dwelling in multivariate model. However, for the clinical significance can be observed in the present results and other literature ^[19, 24], we have some reason to recommend to adopt an appropriate PICC duration to prevent fungal colonization and related CRBSIs.

The present study indicates risk factors for positive PICC tip cultures in preterm infants. It may shed some light on preventing fungal colonization in premature infants in future clinical practice. However, our study also has some disadvantages. First, this is a retrospective study, some bias might exist in patients collection. Second, only a small number of patients in a single-center were enrolled in this study, which might affect the reliability of our study. Thus, large sample multi-center prospective cohort studies should be performed to validate our findings.

In conclusion, from this study population, PICC tips fungal colonization is affected by the postnatal glucocorticoid exposure and duration of PN. In order to prevent fungal colonization and fungemia, clinical management strategies of the above risk factors should be improved.

Materials and methods

Patient selection. This single-center retrospective study was conducted between January 1, 2018 and December 31, 2020. The enrolled infants who underwent ultrasound-guided PICC insertion during hospitalization, were born at < 32 weeks' gestation or birth weight < 1500 grams. The blood culture and catheter tip culture

were performed when the PICC catheters were removed. Exclusive criteria included catheter blockage, accidental detachment, ectopic catheters, twice or more catheterization, and death before catheter removal. The Institutional Review Board of the Affiliated Hospital of Southwest Medical University approved the study protocol (KY2021074). We confirm that all methods were performed in accordance with the relevant guidelines and regulations.

Procedural management of PICC. A 1.9Fr silica gel PICC catheter was inserted into neonates by qualified nurses using ultrasound-guided. An x-ray was obtained to confirm the catheter tip's position in a central vein outside the cardiac silhouette. Dressings were changed 24 hours after catheterization and once a week afterward. However, if the dressings were wet, loose, or both, they were changed immediately. The catheter connector was replaced every week. Only syringes larger than 10 milliliters were used for drug infusion through PICC. PICC catheter was not used for blood draws or transfusions. Tubes were flushed with 2mL of saline every day before infusions were performed^[8].

The definition of outcomes. The tip of the catheter was left 5 cm for pathogen culture after the PICC was removed immediately. Catheter colonization was defined as the distal part of the catheter having pathogens amounting to ≥ 15 colony-forming units (CFU)/tablet, with semiquantitative cultures or pathogens amounting to ≥ 1000 CFU on the quantitative culture. CRBSI was defined when the same pathogen was isolated on quantitative or semiquantitative catheter cultures and other blood cultures, samples of which were obtained through venous drawing^[25].

Data collection. Relevant clinical data from the patients' medical records were separately collected using EpiData (version 3.02) by two researchers. The collected data as following: demographics including gender, gestational age (GA), birth weight (BW), mode of delivery, assisted reproductive technology, twins, and premature rupture of membranes (PROM); PICC related characteristics, including catheter insertion age, indwelling time, and the results of PICC tip cultures; Treatment data contains antibiotic administration, glucocorticoid administration and the duration of parenteral nutrition (PN).

Statistical analysis. Statistical analysis was performed using SPSS 19.0. The

categorical data were described as percentage (%) and compared using chi-square. The continuous data with normal distribution were described as means \pm standard deviation (SD) and compared using student's t-test. The continuous data with abnormal distribution were described as quartiles and analyzed using the rank-sum test. The variables with significant statistical differences were selected into the multivariate model. Due to a strong collinear relationship, the duration of PN and PICC dwelling time was entered into the logistic regression model only one parameter at a time. Gestational age and birth weight were mentioned as important influencing factors in many works of literature [26-28], so they were included in the model for statistics. Then multivariate logistic regression was performed to calculate the adjusted odds ratios (ORs) and 95% confidence intervals (CI). ROC curve was used to determine the optimal cut-off value by calculating the Yoden index.

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Author contributions

Lingping Zhang analyzed the data, wrote the first manuscript. Liu Yang collected data. Wenbin Dong designed the study and contributed to project administration. Xingling Liu and Lianyu Zhang mainly contributes to clinical work, such as PICC puncture and catheter culture preparation. Xiaoping Lei revised the manuscript. All authors reviewed the manuscript.

Additional Information

Competing Interests: The authors declare no competing interests.

Figures

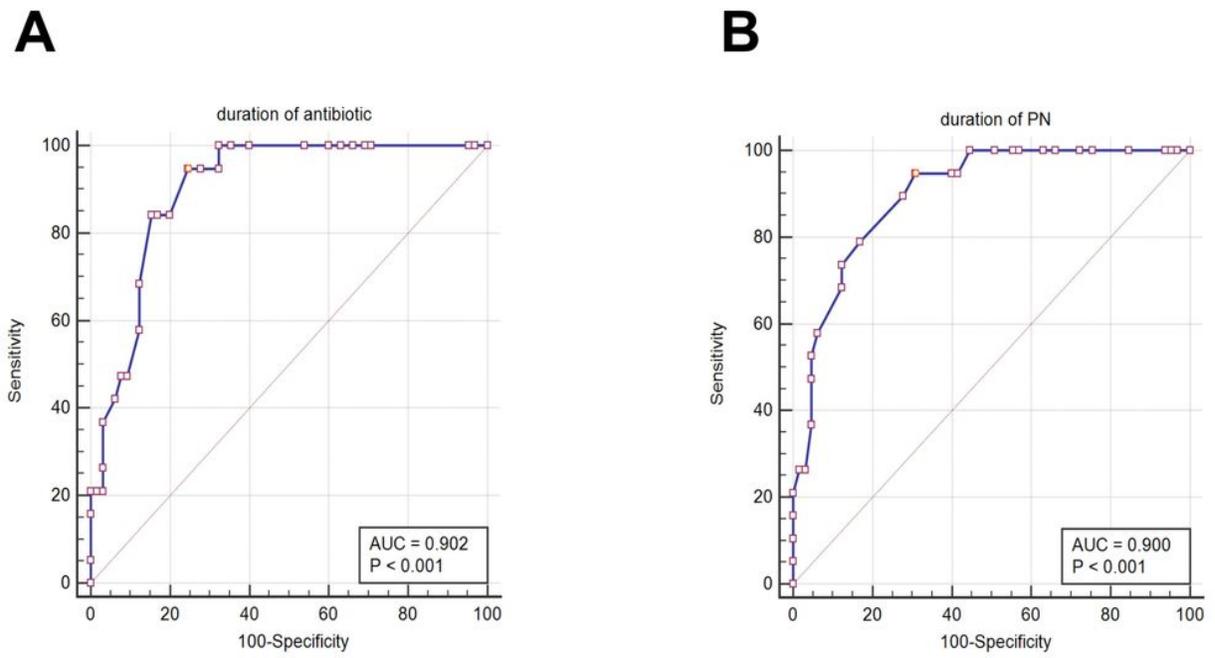


Figure 1

The ROC curve for the duration of antibiotic(A) and PN(B)