A comparison study between *Candida parapsilosis* sepsis and *Candida albicans* sepsis in preterm infants

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In this study, we aimed to investigate the clinical characteristics of *Candida parapsilosis* sepsis in preterm infants. In this retrospective analysis of the clinical data of 11 cases of *Candida parapsilosis* sepsis and 13 cases of *C. albicans* sepsis, the two groups were compared for research using one-way analysis of variance (one-way ANOVA), χ^2 test, and non-conditional logistic regression analysis. Compared to the *C. albicans* sepsis group, the *C. parapsilosis* group demonstrated a significantly lower birth weight (1331.8±252.41 vs. 1721.2±589.08) and significantly longer hospital stay (69.909±20.782 vs. 38.385±19.923) (t'/t = 2.160, -3.787; p=0.045, 0.01, respectively); the incidences of retinopathy of prematurity (ROP) (72.7% vs. 30.8%), tienam administration (72.7% vs. 23.1%), pneumothorax, and thoracic closed drainage (27.3% vs. 0) were higher (χ^2=4.196, 5.916, 4.052; p=0.041, 0.015, 0.044, respectively). Logistic regression analysis indicated only hospital stay and tienam administration in the regression equation (χ^2=18.008, p=0.000). Compared with *C. albicans* sepsis, an average length hospital stay and administration of tienam are the high-risk factors for *C. parapsilosis* sepsis. With regard to the other predisposing factors of preterm infant fungal sepsis, there were no differences between the two groups.

Key words: premature infants, sepsis, Candida parapsilosis, Candida albicans, tienam.

A large number of extremely low birth weight (ELBW) infants now survive in neonatal intensive care units (NICUs) because of the introduction of new medical therapies, such as antenatal steroid administration, postnatal surfactant replacement, the use of intravenous fat emulsions, and improved technological interventional techniques. Unfortunately, the survival of these high-risk infants has been associated with an increase in the incidence of disseminated Candida infections. In recent decades, the trend has been a proportional reduction in *Candida albicans (C. albicans)* and a proportional increase in *C. parapsilosis*, such that *C. parapsilosis* and *C. albicans* now rank first and second, respectively, as causes of Candida sepsis[1-4]. *C. parapsilosis* even ranked above *C. albicans* in some local hospitals of Europe, Asia and South America[5]. *C. parapsilosis* is seen far more than in the past. The reasons for strain changes can be attributed to preterm births and interventions, including an increase in central venous catheters, parenteral nutrition, and widespread long-term application of antibiotics, etc.[6,7]. The prevalence of *C. parapsilosis* candidemia has changed over the years, and now, in some areas, *C. parapsilosis* was the second most common species found in the NICU. The reasons for the rising incidence of *C. parapsilosis* candidemia are not completely known. Both strain types are yeast but have different biological characteristics. What are the differences in the clinical characteristics between *C. parapsilosis* and *C. albicans* sepsis after preterm infants are infected, and what causes these changes? A study on these issues would be helpful in clinical prevention and treatment.

This article is a retrospective research on the clinical characteristics of *C. parapsilosis* septicemia in preterm infants. Procedures were performed according to the Helsinki Declaration and approved by the Institutional Review Board (Institutional Review Board of the General Military Hospital of Beijing PLA). The blood sampling of preterm infants was

Table I. Comparison of the General Condition between the Two Groups

	C. albicans $\bar{x} \pm s$	n	*C. parapsilosis* $\bar{x} \pm s$	n	t/t'	p
Gestational age	31.00±2.769	13	29.546±1.695	11	1.516	0.144
Birth weight	1721.2±589.08	13	1331.8±252.41	11	2.160	0.045*#
Maternal age	28.923±4.291	13	28.727±5.951	11	0.093	0.926
PROM time (h)	26.375±42.315	8	76.60±122.431	5	-1.085	0.301
Apgar scoring						
1 minute	8.308±1.974	13	7.182±2.786	11	1.156	0.260
5 minutes	9.307±1.032	13	8.546±2.162	11	1.071	0.303#
10 minutes	9.846±0.376	13	8.909±1.640	11	1.854	0.091#
Treatment situation						
Hospital days	38.385±19.923	13	69.909±20.782	11	-3.787	0.01*
Fungal infection days	19.00±10.609	13	20.182±12.032	11	-0.222	0.827
Antifungal therapy days	16.714±11.265	13	24.833±10.998	11	-1.309	0.317
Mechanical ventilation days	12.00±4.359	3	22.375±18.852	8	-0.915	0.384

*p<0.05~# equal variances not assumed.
PROM: Premature rupture of membranes.

collected according to the patient's condition after approval was obtained from their families during the hospitalization period.

Material and Methods

A total of 2,721 preterm infants were admitted to preterm infants ICU (with 120 beds) of BaYi Children's Hospital from February 6, 2008 to February 10, 2010. Of the 2,721 admitted preterm infants, 37 (1.36%) were infected with fungal sepsis. The most common culture strains were *C. albicans* (13 cases), followed by *C. parapsilosis* (11 cases), *C. famata* (4 cases), *C. tropicalis* (2 cases), *Monilia guilliermondii* (2 cases), *Cryptococcus laurentii* (2 cases), *C. krusei* (1 case), *C. glabrata* (1 case), and *Aspergillus fumigates* (1 case). All of them were hospital-acquired infection. The histories of the 24 premature infant cases (*C. albicans* and *C. parapsilosis*) were recorded during hospitalization, including fungal infections, clinical manifestations, laboratory examinations, blood culture, sputum culture, and drug sensitivity test results. Perinatal conditions, clinical manifestations, treatment, and prognosis were compared between the *C. albicans* and *C. parapsilosis* sepsis groups.

Diagnostic criteria

Study inclusion criteria of the preterm infants were: a) gestational age <37 weeks; b) two consistent positive blood culture results (Based on clinical manifestations in preterm infants with suspected sepsis, blood samples were collected at the same time from two different parts of the body); and c) clinical onset time of >72 hours after birth. Study exclusion criteria were: a) gestational age ≥37 weeks, b) two inconsistent blood culture results, and c) onset time in the first 48-72 hours after birth.

Fungal culture and antifungal susceptibility testing

Sabouraud culture medium and CHROM agar chromogenic culture medium were provided by microorganisms Science and Technology Co. Ltd. Di Jing, Guangzhou; API20CAUX yeast identification strips and ATBFUNGUS3 antifungal drug susceptibility test were provided from France bioMérieux.

Statistical analysis

statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) software package (version 16.0). Measurement data were expressed as means (±standard deviations). One-way analysis of variance (ANOVA) was used. If analysis

of variance showed a significant difference, for multiple comparisons, LSD method was used if equal variances were assumed and Tamhane's T2 method was used if equal variances were not assumed. Numerical data were expressed with chi-square test. Non-conditional logistic multivariable analysis was carried out to identify differential characteristics of *C. parapsilosis* sepsis. A p value of ≤0.05 was considered statistically significant. All of the p values reported were two-sided.

Results

A comparison of the general condition between *C. parapsilosis* and *C. albicans* sepsis groups is shown in Table I. Only hospital stay and birth weight showed a significant difference between groups. Hospital stay of the *C. parapsilosis* sepsis group was significantly longer than of the *C. albicans* sepsis group, and the lower the birth weight of premature infants, the greater the susceptibility to *C. parapsilosis*. There were no differences in fungal infection time (approximately 20 days) between the two groups. The gestational age, premature rupture of membranes mean time, maternal age, Apgar score, anti-fungal treatment days, and days of mechanical ventilation were similar, with no significant difference.

Comparison of perinatal factors between the two groups

There were no differences between the two groups with respect to perinatal factors such as gender, cesarean section, fetal distress, amniotic fluid contamination, premature rupture of membranes, amniotic chorioamnionitis in the mother, presence or not of fever during pregnancy, and placenta previa, etc. (Table II).

Comparison of clinical data between the two groups

Incidence of retinopathy of prematurity (ROP), usage rate of tienam, pneumothorax, and thoracic closed drainage were higher in the *C. parapsilosis* sepsis group than in the *C. albicans* group, and the differences were statistically significant. We did not find a significant difference in exposure to other risk factors for fungal infection between the groups, such as mechanical ventilation, laser photocoagulation, peripherally inserted central catheter (PICC), bedside ligation of patent ductus arteriosus (PDA), administration of more than three antibiotics, vancomycin, meropenem, pulmonary surfactant application, and clinical manifestations (Table III).

Regression analysis

To further analyze these factors, with occurrence of *C. parapsilosis* sepsis as the dependent variable, an initial screening of the six significant indicators (hospital day, birth weight, pneumothorax, incidence of ROP, administration of tienam, thoracic closed drainage) as covariate variables was conducted, using non-conditional logistic regression analysis. The results indicated that only hospital stay and administration of tienam entered the regression equation (c^2=18.008, p=0.000) (Table IV).

Treatment and prognosis

anti-bacterial treatment: All preterm infants used more than two types of antibiotics, which included mezlocillin, piperacillin, tazobactam, ceftazidime, sulbactam-cefoperazone, tienam, meropenem, vancomycin, teicoplanin, and metronidazole. *Anti-fungal treatment:* Fluconazole was administered 6-40 days and the mean time was 2 or 3 weeks. Only 1 case was fluconazole-resistant, and voriconazole was given instead. Invasive treatments included endotracheal intubation, mechanical ventilation, laser photocoagulation, thoracic closed drainage, PICC, and ligation of PDA. All preterm infants received parenteral nutrition. The rest of the treatment included symptomatic and supportive treatment. Twenty cases were cured (*C. albicans* sepsis group, n=10, *C. parapsilosis* sepsis group, n=10), 3 cases were lost to follow-up (*C. albicans* sepsis group, n=2, *C. parapsilosis* sepsis group, n=1), and 1 case died (*C. albicans* sepsis group). The prognoses were not different between the two groups (c^2=1.175, p=0.556). Secondary meningitis was noted in 1 case and binocular retinal choroiditis in 2 cases in the *C. albicans* sepsis group.

Discussion

In the 1990s, the most striking change was the type of yeast infection causing NICU infection. The most prevalent Candida species that cause candidemias have shifted over time from *C. albicans* to non-albicans Candida spp,

Table II. Comparison of the Two Groups Regarding Perinatal Factors

	C. albicans		*C. parapsilosis*		χ^2	p
	yes	no	yes	no		
Gender Female	4		3		0.035	0.851
Male	9		8			
Cesarean section	5	8	5	6	0.120	0.729
Fetal distress	1	12	4	7	2.970	0.085
Amniotic fluid contamination	2	11	2	9	0.034	0.983
Pregnancy- antibiotics use	0	13	1	10	1.233	0.267
Pregnancy- fever	0	13	2	9	2.579	0.108
Amniotic membrane chorioamnionitis	3	10	1	10	0.839	0.360
PROM	8	5	5	6	0.621	0.431
Placenta previa	0	13	1	10	1.233	0.267
Oligohydramnios	0	13	1	10	1.233	0.267

PROM: Premature rupture of membranes.

including *C. parapsilosis*, *C. tropicalis* and *C. glabrata*. This is in agreement with literature reports that invasive candidemia disease caused by non-albicans Candida spp has sustained an increase [8], indicating that non-albicans Candida spp infection has become the predominant fungal pathogen in many NICUs. *C. parapsilosis* accounted for one-fourth of all cases of invasive fungal infection in very low birth weight (VLBW) infants. Our results show that *C. parapsilosis* sepsis is the second most common Candida species isolated from bloodstream infections, consistent with the reported literature[1-4]. It is related only minimally with perinatal factors because it is a hospital-acquired infection. Birth weight and hospital stay demonstrated significance differences between the two groups. The lower the birth weight and the longer the hospital stay, the greater the susceptibility to infection with *C. parapsilosis* sepsis, but birth weight did not enter the regression equation. In their study of *C. albicans* and *C. parapsilosis* infections, Kristóf et al.[9] found that birth weight, gestational age <30 weeks and cesarean section demonstrated significant differences. The two species of fungi with respiratory colonization were the same between the ELBW and VLBW groups. The proportions of candidemias caused by *C. albicans* and *C. parapsilosis* were 9:7 in the ELBW group, 6:3 in the VLBW group, and 15:1 in the >1500 g group. The mortality rate of *C. parapsilosis* was higher than of *C. albicans*. Clerihew et al.[10] reported that C. parapsilosis is a less deep-seated infection, and mortality was similar compared with *C. albicans*. Our results showed that *C. parapsilosis* sepsis is unrelated to cesarean section. There was no difference in prognosis between the two groups, and only one case died of *C. albicans* sepsis. Saiman et al.[11] found that preterm infants with a hospital stay in the NICU of more than 7 days and 14 days might suffer from fungemia sepsis, but there was no statistically significant difference with stays of more than 21 days. Hernández-Castro[12] found that average age of neonatal infection with *C. parapsilosis* was 13.6 days. Sarvikivi [13] described a clonal outbreak caused by *C. parapsilosis* in the NICU during a 12-year period and the development of fluconazole resistance of the causative clone during the long-term use of fluconazole prophylaxis. Prematurity and LBW as well as prolonged umbilical catheterization were identified as risk

Table III. Comparison of the Two Groups Regarding Clinical Data

	C. albicans		*C. parapsilosis*		χ^2	p
	yes	no	yes	no		
Clinical Manifestation						
Frequent apnea	5	8	6	5	0.621	0.431
Poor response	3	10	4	7	0.509	0.476
Poor skin perfusion	4	9	2	9	0.503	0.478
Excessive phlegm	2	11	0	11	1.846	0.174
Difficult to withdraw ventilator	2	1	1	7	0.410	0.522
Underlying Disease						
NRDS	9	4	8	3	0.035	0.851
Pneumonia of newborn	9	4	6	5	0.548	0.459
Pneumothorax	0	13	3	8	4.052	0.044*
NEC	0	13	2	9	2.579	0.108
Intracranial hemorrhage	1	12	3	8	1.645	0.200
ROP	4	9	8	3	4.196	0.041*
Treatment~						
Vancomycin	3	10	2	9	0.087	0.769
Meropenem	2	11	2	9	0.034	0.855
Tienam	3	10	8	3	5.916	0.015*
Sulperazon	6	7	4	7	0.235	0.628
Three antibiotics combined	8	5	4	7	1.510	0.219
Pulmonary surfactant	7	6	7	4	0.235	0.628
Mechanical ventilation	3	10	8	3	0.336	0.562
Laser photocoagulation	1	12	1	10	0.015	0.902
Thoracic closed drainage	0	13	3	8	4.052	0.044*
PICC	1	12	1	10	0.015	0.902
Patent ductus arteriosus - bedside ligation	0	13	2	9	2.579	0.108

*p<0.05

NRDS: Neonatal respiratory distress syndrome. NEC: Necrotizing enterocolitis. ROP: Retinopathy of prematurity. PS: Pulmonary surfactant. PICC: Peripherally inserted central catheter.

factors for *C. parapsilosis* bloodstream infections. A clear increase in the length of hospital stay and the duration of mechanical ventilation were seen in the neonates with *C. parapsilosis* bloodstream infections. Our results indicated that timing of fungal infection was similar between the two groups, at approximately 20 days, and hospital stay in the *C. parapsilosis* sepsis group was significantly longer than in the *C. albicans* group, but there was no difference in the duration of mechanical ventilation.

Laboratory studies have documented that *C. parapsilosis* is less virulent than *C. albicans* in animal models of infection[14]. However, several factors have been identified that give *C. parapsilosis* a selective advantage in the hospital environment, such as its capability to adhere tenaciously to prosthetic materials and to proliferate rapidly in high concentrations of glucose. Moreover, the propensity of clinical isolates of *C. parapsilosis* to form extensive biofilm in glucose-containing solutions suggests that this trait may contribute to its ability to adhere to plastic catheters and cause systemic infections in premature newborns being treated with total parenteral nutrition, blood pressure transducers, or other invasive devices. Repeated observations have documented that *C. parapsilosis* candidemia can occur in the absence of prior detectable colonization and/or symptomatic infection in other body sites of the same infant, usually by means of horizontal transmission through contamination by exogenous articles such as medical facilities or liquid, the hands of health care personnel, prosthetic devices,

Table IV. Non-Conditional Logistic Regression Analysis of Factors Related with C. parapsilosis Sepsis

factor	B	SE	Wald	P	OR	95% CI for OR	
						upper	lower
Hospital stay	0.125	0.057	4.761	0.029	1.134	1.269	1.013
Administration of tienam	3.975	2.468	2.495	0.107	52.275	671.6	0.423

CI: Confidence interval. OR: Odds ratio.

and catheters[15]. Although all preterm newborns were treated in the same ward and exposed similarly to cross-infection through the hands of the nurses, horizontal transmission of fungemia occurred only in the newborn with a serious defect in cutaneous barrier integrity. Previous observation was in agreement with the general view that, in NICUs, *C. parapsilosis* outbreaks were mainly due to deliberate disruption of the cutaneous barrier for administration of invasive therapies and use of monitoring equipment[16]. There were 3 cases each of pneumothorax and thoracic closed drainage in the *C. parapsilosis* sepsis group compared to 0 cases each in the *C. albicans* sepsis group, and among 12 cases with ROP, 8 (66.7%) cases were infected with *C. parapsilosis*, and the differences between the groups were significant. However, the other high-risk factors of fungal infection, such as mechanical ventilation, tracheal intubation, PICC, bedside ligation of PDA, laser surgery, and PS application showed no differences between the two groups. Therefore, procedural operations with respect to every aspect of thoracic closed drainage and ROP screening should be strict.

Compared with the *C. albicans* sepsis group, it seemed more likely to have apnea (54.5%: 38.5%) and poor response (36.4%: 6%) in the *C. parapsilosis* sepsis group, but there were no differences between the two groups regarding other manifestations, such as poor skin perfusion, excessive phlegm, blood oxygen saturation instability, or difficulty in ventilator withdrawal, which were non-specific manifestations of fungal or bacterial infections. It was at times difficult to define *C. parapsilosis* infections according to the clinical manifestations, because these infants often had overlapping respiratory, intracranial, gastrointestinal, and infectious illnesses. The manifestations of *C. parapsilosis* sepsis were gentle and less prone to acute lethal manifestations, and this group had no death.

A previous study also suggested that prolonged third-generation cephalosporin use predisposes to *C. parapsilosis* infections in VLBW infants[17]. Several applications of antibiotics were analyzed in this group, and the results indicated that there were no differences between the two groups regarding the several different antibiotics used, such as meropenem, vancomycin, and sulperazon, or three antibiotics combined. However, the administration of tienam is a risk factor for *C. parapsilosis* infections and entered the regression equation. Tienam (imipenem and cilastatin sodium, MSD) is a broad-spectrum β-lactam antibiotic and a potent inhibitor of bacterial cell wall synthesis and it is bactericidal against a broad spectrum of pathogens—gram-positive and gram-negative, aerobic and anaerobic. It is resistant to degradation by bacterial beta-lactamases, which makes it active against a high percentage of organisms such as *Pseudomonas aeruginosa*, Serratia spp, and Enterobacter spp, which are inherently resistant to most beta-lactam antibiotics. The antibacterial spectrum of tienam is broader than that of any other antibiotic studied. The main side effects of tienam are liver function changes, thrombophlebitis and neutropenia. There was too low a number to document a relation between tienam and *C. parapsilosis*, so we speculate that the relation between the administration of tienam and *C. parapsilosis* infection may be related with neutropenia. Further prospective research is needed to explore this possibility.

In conclusion, compared with the *C. albicans* sepsis group, the average hospital stay and administration of tienam were shown to be the high-risk factors for *C. parapsilosis* sepsis. The other predisposing factors of fungal septicemia demonstrated no differences between the two groups.

Study Limitations

The sample of this study was too small to analyze the possible sources of *C. parapsilosis* infection. For such a study, it would be necessary to expand the sample size or conduct animal experiments for an in-depth study of the effects of duration of tienam administration and administration method, pharmacokinetics, and how to determine susceptibility to *C. parapsilosis*.

REFERENCES

1. Kuzucu C, Durmaz R, Otlu B, et al. Species distribution, antifungal susceptibility and clonal relatedness of Candida isolates from patients in neonatal and pediatric intensive care units at a medical center in Turkey. New Microbiol 2008; 31: 401-408.
2. Hinrichsen SL, Falcão E, Vilella TA, et al. Candidemia in a tertiary hospital in northeastern Brazil. Rev Soc Bras Med Trop 2008; 41: 394-398.
3. Pfaller MA, Castanheira M, Messer SA, et al. Variation in Candida spp. distribution and antifungal resistance rates among bloodstream infection isolates by patient age: report from the SENTRY Antimicrobial Surveillance Program (2008-2009). Diagn Microbiol Infect Dis 2010; 68: 278-283.
4. Aydin F, Bayramoglu G, Guler NC, et al. Bloodstream yeast infections in a university hospital in Northeast Turkey: a 4-year survey. Med Mycol 2011; 49: 316-319.
5. Trofa D, Gácser A, Nosanchuk JD. Candida parapsilosis, an emerging fungal pathogen. Clin Microbiol Rev 2008; 21: 606-625.
6. Medrano DJ, Brilhante RS, Cordeiro Rde A, et al. Candidemia in a Brazilian hospital: the importance of Candida parapsilosis. Rev Inst Med Trop Sao Paulo 2006; 48: 17-20.
7. Chang MR, Correia FP, Costa LC, et al. Candida bloodstream infection: data from a teaching hospital in Mato Grosso do Sul, Brazil. Rev Inst Med Trop Sao Paulo 2008; 50: 265-268.
8. Pappas PG, Rex JH, Sobel JD, et al. Infectious Diseases Society of America. Guidelines for treatment of candidiasis. Clin Infect Dis 2004; 38: 161-189.
9. Kristóf K, Janik L, Komka K, et al. Clinical microbiology of neonatal candidiasisin Hungary. Acta Microbiol Immunol Hung 2010; 57: 407-417.
10. Clerihew L, Lamagni TL, Brocklehurst P, et al. Candida parapsilosis infection in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 2007; 92: F127-129.
11. Saiman L, Ludington E, Pfaller M, et al. Risk factors for candidemia in Neonatal Intensive Care Unit patients. The National Epidemiology of Mycosis Survey study group. Pediatr Infect Dis J 2000; 19: 319-324.
12. Hernández-Castro R, Arroyo-Escalante S, Carrillo-Casas EM, et al. Outbreak of Candida parapsilosis in a neonatal intensive care unit: a health care workers source. Eur J Pediatr 2010; 169: 783-787.
13. Sarvikivi E, Lyytikäinen O, Soll DR, et al. Emergence of fluconazole resistance in a Candida parapsilosis strain that caused infections in a neonatal intensive care unit. J Clin Microbiol 2005; 43: 2729-2735.
14. Weems JJ Jr. Candida parapsilosis: epidemiology, pathogenicity, clinical manifestations, and antimicrobial susceptibility. Clin Infect Dis 1992; 14: 756-766.
15. Trofa D, Gácser A, Nosanchuk JD. Candida parapsilosis, an emerging fungal pathogen. Clin Microbiol Rev 2008; 21: 606-625.
16. Lupetti A, Tavanti A, Davini P, et al. Horizontal transmission of Candida parapsilosis candidemia in a neonatal intensive care unit. J Clin Microbiol 2002; 40: 2363-2369.
17. Benjamin DK Jr, Ross K, McKinney RE Jr, et al. When to suspect fungal infection in neonates: a clinical comparison of Candida albicans and Candida parapsilosis fungemia with coagulase-negative staphylococcal bacteremia. Pediatrics 2000; 106: 712-718.