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Nosocomial Outbreak of *Candida parapsilosis* sensu stricto Fungemia in a Neonatal Intensive Care Unit in China

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Running head: Outbreak of *C. parapsilosis* fungemia

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Summary

Background

*Candida parapsilosis* is a common agent of fungemia, but few outbreaks of *Candida parapsilosis* infection have been reported in China.

Aim

This study aimed to elaborate an outbreak of nosocomial *Candida parapsilosis sensu stricto* fungemia in a neonatal intensive care unit (NICU) of a comprehensive hospital in China from July to October 2017.

Methods

Epidemics and characteristics of fungemia cases were investigated. Surveillance samples were collected. VITEK 2 Compact System, internal transcribed spacer sequencing, and Random Amplified Polymorphic DNA (RAPD) typing were conducted to identify the isolates. Antifungal susceptibility test was performed for all bloodstream isolates.

Findings

Sixteen neonates were diagnosed as *Candida parapsilosis sensu stricto* fungemia during this period. Presenting symptoms included leukopenia, thrombocytopenia, and respiratory crackles. Fifteen cases were cured while one case who suffered from severe concomitant diseases died. The isolates were susceptible to fluconazole, amphotericin B, itraconazole, voriconazole, and 5-fluorocytosine. A total of 313 surveillance samples were collected, and *Candida parapsilosis sensu stricto* was identified from 16 environmental samples and one sample from an ultrasonographer’s
hand. The colonized locations included wiping cloths, faucets, sinks, operating table, puddles in the bathroom, a ventilator, and an ultrasonic probe. The RAPD patterns of all the *Candida parapsilosis* sensu stricto isolates from bloodstream and surveillance samples were identical. The outbreak was controlled after a series of infection control measures.

**Conclusions**

Contaminated environment was associated with this outbreak. Close attention to immunocompromised patients, thorough environmental disinfection and hand hygiene should be strengthened in NICU.

**Keywords:**

*Candida parapsilosis*, neonatal intensive care unit, nosocomial infection, environmental contamination, outbreak control
Introduction

Candida species has been a major cause of nosocomial infections since the 1990s[1]. *Candida parapsilosis (C. parapsilosis)* is one of the most common *Candida* species that cause invasive disease, and the incidence of *C. parapsilosis* infection has significantly increased over the past decade[2]. A laboratory-based surveillance of candidaemia in 25 hospitals in Asian countries showed that *C. parapsilosis* accounted for 12.1% of 1,910 blood isolates evaluated [3]. Before 2005, *C. parapsilosis* was divided into three groups, I to III [4]. Genetic studies show that these three groups are three closely related but distinct species: *C. parapsilosis sensu stricto*, *C. orthopsilosis*, and *C. metapsilosis* [5]. As commercial systems and traditional phenotyping test are not sufficient to differentiate these species, they are called *C. parapsilosis* complex in some studies [6].

*C. parapsilosis* is one of the most common causative agents of candidaemia in a neonatal intensive care unit (NICU) and has caused numerous outbreaks in neonates [7-10]. The reported risk factors of *C. parapsilosis* candidaemia in NICU patients include low birth weight [11], immature skin structure [12], prolonged use of antibiotics [13], indwelling central or umbilical venous catheters [14], parenteral nutrition [15], and mechanical ventilation [16]. Contamination of health care workers' (HCWs) hands is considered one of the main sources of candidaemia outbreaks in NICUs [17, 18]. Few outbreaks of *Candida parapsilosis* infection have been reported in China. An outbreak of *C. parapsilosis* fungemia in the NICU of a hospital in Hebei
province of China has been reported, but only involved four preterm infants [19].

From 20\textsuperscript{th} July to 31\textsuperscript{st} October 2017, 16 cases of fungemia caused by \textit{C. parapsilosis} sensu stricto were identified in a NICU of a tertiary care hospital in Beijing, China. The department generally admitted neonates with gestational weeks between 28 and 32.

At the end of September 2017, an outbreak of \textit{C. parapsilosis sensu stricto} fungemia was suspected and a detailed epidemiological investigation of this outbreak was conducted. The purposes of this outbreak report were: (i) to construct the epidemic curve, by clinical characterization of the causative agents in the outbreak; (ii) to search for the potential source of this outbreak; (iii) to explore the intervention measures required and provide advice for the prevention and control of future, similar outbreaks.
Materials and methods

Study design and setting. This was an ambidirectional study conducted in an 80-bed NICU of a tertiary hospital. A protocol for epidemiological investigation was designed at the end of September 2017. Data for each patient were obtained through reviewing microbiology lab results and medical records. Intervention programs were prompted by the results of investigation and environmental screening. This study was approved by the institutional ethics committees of The Army General Hospital, Beijing, China. As all the data were collected and analysed anonymously, the requirement for informed consent was waived.

Sampling of environmental surface, HCWs, and neonatal patients, and fungal culture. A total of 264 environmental samples from locations including infant incubators (ATOM INFANT INCUBATOR V-2100G, Atom Medical Corporation, Tokyo, Japan), operating tables, frequently touched instruments, indwelling devices, wiping cloths and faucets were collected in September and October 2017 using microbiological transport swabs (Guangzhou Improved Medical Instruments Co., Ltd., Guangzhou, China). Fourteen samples from hands of HCWs and 35 samples from the axillae and groins of neonatal patients were also collected. The sample collection procedure was conducted according to the instructions of the product. Specimens were inoculated onto Sabouraud Dextrose Agar plate with chloramphenicol (OXOID, Thermo Fisher biochemical products Co., Ltd. Beijing, China) for subsequent culture of Candida.
species. Cultures were considered negative if no growth occurred after 21 days of incubation.

**Identification of C. parapsilosis complex, antifungal susceptibility test and Random Amplified Polymorphic DNA (RAPD) typing.** The phenotypic characterization of the isolates was identified by the morphology of colonies and their characteristic growth on chromogenic medium (CHROMagar Microbiology, Paris, France) [20]. All suspected isolates were identified using the VITEK 2 Compact System. C. parapsilosis sensu stricto and C. metapsilosis were distinguished by internal transcribed spacer (ITS) sequencing as previously described [5]. The *in vitro* susceptibility of bloodstream isolates to fluconazole, amphotericin B, itraconazole, voriconazole, and 5-fluorocytosine was determined using the antifungal susceptibility test for yeasts (ATB FUNGUS 3, bioMérieux SA, France). RAPD typing was conducted on all clinical and environmental C. parapsilosis complex isolates [5].

**Infection-related outcomes.** The incidence of C. parapsilosis sensu stricto fungemia was used as the primary outcome. The denominators referred to the numbers of admissions to the NICU ward.

**Intervention.** Once an outbreak was suspected three major infection control measures were implemented: (i) cohorting of the fungemia cases from non-fungemia cases in a specified area of the department; (ii) enhanced environmental sampling and
screening of HCWs and patients for contamination with *C. parapsilosis* complex; (iii) education of HCWs to improve hand hygiene compliance. The educational practices included informing all HCWs on NICU of the outbreak, presenting information on severe cases during the outbreak in relation to hand contamination, and emphasizing the need of strict hand washing procedure using Jifro Hand Antiseptic Rinse Free Gel (Shanghai Likang Disinfectant Hi-Tech Co., Ltd, Shanghai, China) following all patient contacts as advised by the WHO 5 Moments for Hand Hygiene.

After the identification of environmental contamination, three more measures were implemented: (i) enhanced environmental disinfection. The bathroom was disinfected and redecorated with new sinks, sewer pipes and ceramic tiles. Equipment in the ultrasonography department was disinfected. (ii) For environmental surface cleaning, reusable microfiber wiping cloths which would be disinfected using sodium dichloroisocyanurate (AIERSHI, Shanghai Likang Disinfectant Hi-Tech Co., Ltd, Shanghai, China) were changed to disposable commercial disinfectant wipes (X-Joyclean, Shijiele Technology Co., Ltd, Beijing, China). (iii) Refresher education to cleaners on the correct techniques for disinfection of the wiping cloths. After the outbreak was terminated, we switched back to using the reusable wiping cloths after strict disinfection procedures, due to the high cost of disposable commercial disinfectant wipes. Additionally, prophylactic antifungal therapy with intravenous fluconazole was given to high-risk neonates. No new case of *C. parapsilosis* sensu stricto fungemia was detected after 1st November.
Results

Epidemics and characteristics of the patients. The first case of *C. parapsilosis* sensu stricto fungemia was detected on 20th July. The patient was a 12-day-old premature neonate. Prior to fungemia, the patient had received broad spectrum antibiotics (piperacillin/tazobactam and imipenem) for 12 days and fluconazole for five days. He was noted to have hypoactive bowel sounds, thrombocytopenia and leucocytosis before his blood culture yielded *C. parapsilosis* sensu stricto. The second and third fungemia patients were identified 21 days after the first case was diagnosed. The fourth to seventh cases were detected between 12th and 15th September. An epidemiological investigation was initiated at the end of September. Between 20th July and 31st October, a total of 166 patients were admitted and treated in the NICU department for at least 48 hours. Among these patients, sixteen patients (9.64%) were diagnosed with *C. parapsilosis* sensu stricto fungemia, and 13 cases occurred within eight weeks, prior to the end of the outbreak. The epidemic curve of *C. parapsilosis* sensu stricto fungemia in the entire hospital in 2017 is shown in Figure 2.

The epidemiological and clinical characteristics of the 16 cases of fungemia are presented in Table I. Eleven cases (68.8%) were male. Nine cases (56.2%) were delivered by caesarean section. The median gestational age and birth weight of these infants were 30 weeks (range 28 to 31 weeks) and 1580 g (range 990 to 1800 g), respectively. The ages of the patients at the onset of fungemia ranged from two to 38
days after admission. Nonspecific signs were noted among the fungemia cases, including leukopenia (WBC counts < 15×10^9/L, ten cases, 62.5%) thrombocytopenia (platelet counts < 100×10^9/L, seven cases, 43.8%), hypoactive bowel sounds (four cases, 25.0%), crackles (three cases, 18.8%) and respiratory harshness (two cases, 12.5%). Two patients did not present any abnormal symptom and sign. None of the fungemia cases had concomitant bacteraemia. Fluconazole treatment was administered according to Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America [21]. Fifteen of the 16 patients were cured. One female neonate did not significantly improve following fluconazole treatment. She also suffered from severe concomitant diseases including intracranial haemorrhage, respiratory failure, congenital heart disease, septicaemia and deformity of both hands. After six days of treatment the patient died.

**Identification of *C. parapsilosis* strains from clinical and environmental samples.** Seventeen out of 264 environmental surveillance cultures yielded *C. parapsilosis* sensu stricto, including samples from three wiping cloths in the cleaner room, faucets, sinks, operating table, puddles, one wiping cloth in the bathroom, a ventilator, and an ultrasonic probe. The pathogen was also isolated from the hand of an ultrasonographer on duty in NICU. Cultures from hands of HCWs in the department did not yield *C. parapsilosis* sensu stricto. Cultures of axilla and groin of neonates yielded no *C. parapsilosis* sensu stricto. Another 23 surveillance cultures yielded *C. metapsilosis*. These samples were collected from a sink in the cleaner’s room, negative.
pressure suction tubes, inner wall of incubators, nasal mask, condensed water of a ventilator, humidifying water of an incubator, a disinfectant container, and a medical adhesive tape. Cultures of samples from the axilla or groin of nine neonates, including four *C. parapsilosis* sensu stricto fungemia cases, also yielded *C. metapsilosis*. Figure 1 shows the hospital ward layout and the location of surveillance samples where *C. parapsilosis* sensu stricto and *C. metapsilosis* were detected.

The susceptibility of the bloodstream isolates to antifungal agents and RAPD typing of isolates from clinical and environmental sources. All the bloodstream *C. parapsilosis* sensu stricto isolates exhibited low resistance to five tested antifungal agents. The MIC values of fluconazole, amphotericin B, itraconazole, voriconazole, and 5-fluorocytosine for bloodstream isolates were 1 mg/mL, 0.5 mg/mL, 0.125 mg/mL, 0.06 mg/mL, and 4 mg/mL, respectively. Figure 3 illustrates RAPD banding patterns of representative isolates from clinical and environmental sources. A total of three RAPD profiles were detected among all the isolates. RAPD patterns of the *C. parapsilosis* sensu stricto isolates from both bloodstream and environment were identical (profile A). Most *C. metapsilosis* isolates cultured from surveillance samples showed similar patterns (profile B). A patient in NICU was diagnosed as fungemia on 1st November which was identified as *C. metapsilosis* and had a similar RAPD pattern to the *C. metapsilosis* isolates detected from surveillance samples (lane 6). Only one *C. metapsilosis* isolate detected from a sink in the cleaner’s room showed a different RAPD pattern (profile C).
Discussion

This report describes an outbreak of *C. parapsilosis* sensu stricto fungemia in a NICU. *C. parapsilosis* has been reported to be the predominant fungal pathogen that causes bloodstream infections among very-low-birth-weight infants (birth weight < 1500 g) in NICUs [22, 23]. *C. parapsilosis* sensu stricto is the most prevalent *C. parapsilosis* species in both superficial and invasive human infections [4, 24-29]. In our study a total of 16 neonates (9.64%) were infected with *C. parapsilosis* sensu stricto. Identical RAPD patterns and antifungal susceptibility test results suggested a common source of this outbreak. One neonate who also suffered from severe concomitant diseases died. There was no direct evidence that the death was caused by the nosocomial fungal infection, but it complicated the clinical picture and led to additional healthcare costs.

Premature infants are more susceptible to *Candida* infections due to the immature immune system and an immature skin which is not an efficient barrier to *Candida* [30, 31]. In this outbreak, premature neonates in the NICU were also frequently exposed to the reported risk factors because of concomitant diseases such as neonatal respiratory distress syndrome, acidosis, anaemia, neonatal jaundice, and extrusion injury. All of the fungemia cases received clinical interventions including mechanical ventilation, indwelling cannulae, nasogastric tubes, as well as bedside ultrasonography and X-ray examination. All neonates were treated with antibiotics and 87.5% received parenteral nutrition (data not shown). A case-control study was conducted to
compare the infected neonates with a control group for their exposure to these risk factors but no significant differences were found. This indicates that neonates in the NICU were frequently exposed to the risk factors, and thus they were all at high risk of *C. parapsilosis* sensu stricto infection in the presence of environmental contamination.

Presenting symptoms of the fungemia cases were nonspecific, which is identical to the findings of previous studies that also reported variable and vague clinical signs in fungemia patients including feeding intolerance, hyperthermia, dyspnoea, and low platelet and white blood cell counts [19, 32]. Atypical and variable symptoms increased the difficulty of diagnosis.

The 16 neonates were born in different hospitals. No common delivery environment or inter-hospital transfer methods were observed. In the NICU, each neonate was placed in an individual incubator that was distributed randomly across different areas of the department. Hence there was no direct evidence of patient-to-patient transfer. The contamination of several locations in the bathroom might have contributed to the outbreak. *C. parapsilosis* sensu stricto might have been transferred to neonates on the hands of HCWs and caused fungemia. Previous studies have shown a correlation between *C. parapsilosis* nosocomial infection and contaminated environments including vacuum systems [33], toilet floor [34], sink and air-conditioning vents [35]. García-Martos P. reported otomycosis caused by *C. parapsilosis* due to sea bathing [36]. Our study reinforces the importance of cross-infection from water sources for *C.*
parapsilosis sensu stricto infection in NICU. The three colonized wiping cloths in the cleaner’s room might also have played a role in the spread of the pathogen because they were used on locations like switches and doorknobs. The colonized ultrasonic probe and the hand of an ultrasonographer on duty in NICU also highlighted the possibility that ultrasonic examination is a way of fungal cross-transmission.

Although no C. parapsilosis sensu stricto was detected on hands of HCWs in the NICU department, we cannot exclude the scenario that the HCWs may have been transiently colonized by the pathogen that was not detected by our sampling methods. Contaminated hands of HCWs have been shown to be the source of C. parapsilosis outbreaks in other studies [2, 12, 37, 38]. The isolation of the organism from an ultrasonographer’s hand further highlights the importance of hand hygiene including those from outside the department.

We discriminated C. parapsilosis sensu stricto and C. metapsilosis by ITS sequencing. In our surveillance, C. metapsilosis colonization was detected in both the environment and skin cultures. The neonate diagnosed as C. metapsilosis fungemia on 1st November put forward the possibility that this pathogen can also cause bloodstream infection, although it did not lead to an outbreak. Four C. parapsilosis sensu stricto fungemia cases were C. metapsilosis positive, indicating that the pathogenicity of C. parapsilosis sensu stricto was greater than that of C. metapsilosis. Previous studies have shown that C. metapsilosis is very rarely isolated from clinical samples [39] and is
less virulent than *C. parapsilosis* sensu stricto [40]. The evolution of *C. metapsilosis* is probably associated with a nonmammalian environment [17].

The outbreak was terminated with implemented of additional infection control measures. More importantly, we identified the source of transmission by environmental sampling as well as screening of HCWs and patients for colonization. Targeted disinfection of locations contaminated with *C. parapsilosis* sensu stricto as well as education of HCWs and staff about hand hygiene and disinfection techniques might have been key to the outbreak control. The locations colonized with *C. parapsilosis* sensu stricto were mostly water-related such as wiping cloths, faucet, sink, and puddles on the table. Direct contact with water-related environments and medical instruments can be a route of fungi transmission and should be considered in the control of candida outbreaks. The colonized surface of one ventilator also revealed the incompleteness of environmental disinfection. Our findings reinforce the importance of adequate environmental disinfection in the hospital. Additionally, for neonates showing atypical symptoms, early and accurate diagnosis is also required to control the outbreak.

**Conclusions**

This study described a nosocomial outbreak of *C. parapsilosis* sensu stricto fungemia in a NICU in China. *C. metapsilosis* colonization was also detected in NICU but did not
lead to an outbreak. Incomplete environmental disinfection may have been the main reason for the outbreak. A quick response with environmental surveillance and comprehensive interventions were crucial to the effective control of the outbreak. Our findings emphasizes the necessity of adequate disinfection of the environment and hand hygiene in the hospital.
Acknowledgment

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.
References


Table I. Demographic and clinical characteristics of 16 patients with *C. parapsilosis* sensu stricto fungemia

<table>
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<th>Case No.</th>
<th>GA (wk)/sex</th>
<th>BW (kg)</th>
<th>Apgar score at 5 min</th>
<th>Onset of fungemia (y/m/d)</th>
<th>Age when fungemia was diagnosed (d)</th>
<th>WBC count ($\times 10^9$/L)</th>
<th>Platelet count ($\times 10^{12}$/L)</th>
<th>Broad spectrum antibiotics use before fungemia</th>
<th>Length of treatment with FLUCZ (d)</th>
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GA = gestational age; F = female; M = male; BW = birth weight; WBC = white blood cell; TZP = piperacillin/tazobactam; IPM = imipenem; P = penicillin; VA = vancomycin; AK = amikacin; FLUCZ = fluconazole.
Figure Legends

Figure 1. Schematic map of the NICU and the location of surveillance samples from which *Candida parapsilosis* complex isolates were identified. The rectangular shadows represent incubators. The red dots represent *Candida parapsilosis* sensu stricto isolates, sampled from locations including three wiping cloths in the cleaner room, faucets, sinks, operating table, puddles, and one wiping cloth in the bathroom. The green dots represent *Candida metapsilosis* isolates sampled from environment locations including a sink in the cleaner room, negative pressure suction tubes, inner wall of incubators, a nasal mask, condensed water of a ventilator, humidifying water of an incubator, a disinfectant container, and a medical adhesive tape. The green triangles represent *Candida metapsilosis* isolates sampled from skin cultures of neonates. Other locations that were sampled but did not detect *Candida parapsilosis* complex colonization are not marked in the figure. Incubators were portable and were often moved, hence the position of each incubator when the outbreak occurred is not available.

Figure 2. Epidemic curve of *Candida parapsilosis* sensu stricto fungemia in the hospital in 2017. A marked increase in the number of cases was noted during the outbreak period. After the outbreak was halted at the end of October, the number of cases decreased. In November and December, no *Candida parapsilosis* sensu stricto fungemia was detected. The other three departments where bloodstream infection with *Candida parapsilosis* sensu stricto occurred in chronological order were Department of Paediatric Surgery, Department of Very Preterm Infants and
Department of Neurology, respectively.

**Figure 3. RAPD typing of eight representative clinical and environmental *Candida parapsilosis* complex isolates.** Lanes 1-8: lane 1-2, bloodstream *C. parapsilosis* sensu stricto isolates; lane 3-4, environmental *C. parapsilosis* sensu stricto isolates; lane 5 and 7, environmental *C. metapsilosis* isolates; lane 6, bloodstream *C. metapsilosis* isolate; lane 8, an environmental *C. metapsilosis* isolate from a sink in the cleaner room. M, 100 bp ladder marker.
A bar chart showing the number of new cases over different months. The chart compares the number of cases in the NICU (solid black bars) and other departments (hatched bars). The x-axis represents the months from January to December, and the y-axis represents the number of new cases, ranging from 0 to 10.