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Candida utilis candidaemia in premature infants: a retrospective single-centre study

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ABSTRACT

This retrospective study was conducted in a neonatal intensive care unit in Beijing. Patients whose blood culture yielded *Candida utilis* during hospitalisation from January 2009 to December 2017 were enrolled. Thirteen preterm infants of median gestational age 29.85 weeks were included. Laboratory tests on the day of onset showed thrombocytopaenia in 11 patients, granulocytopaenia in eight and elevated C-reactive protein in seven. No fungal endophthalmitis, renal infection, carditis or involvement of other end organs was observed in any of the cases. All 13 patients were cured after fluconazole therapy.

Preterm neonates in neonatal intensive care units (NICUs) are at high risk of undergoing various invasive procedures together with immature immunity. They are more likely to develop nosocomial infections, including fungal septicaemia.[1 2] *Candida* species have become the third most common pathogens for late-onset septicaemia in newborn infants and are associated with a mortality rate of 20–34%.[3] However, *Candida utilis* is seldom reported as the cause of candidaemia in humans.[4] As a result, there is a lack of reliable information about its clinical features, treatment and prognosis. In the present study we performed a retrospective review of premature infants with *C. utilis* candidaemia (CUC) occurring in our NICU.

The retrospective study was conducted in the NICU of a public hospital in Beijing. Patients with CUC (see online Appendix) during hospitalisation were enrolled. Data including demographic characteristics, medical history, invasive procedures, medications, laboratory data and outcomes were collected.

From January 2009 to December 2017, CUC occurred in 13 premature infants (0.16%) out of a total of 79 863 neonates admitted to the NICU. The mean±SD birth gestational age of the 13 preterm infants with CUC was 29.85±1.14 weeks and the mean±SD birth weight was 1329.23±409.05 g (table 1).

The clinical manifestations are shown in table 2, the most frequent signs being poor response (9/13) and SaO_2 instability (11/13). In the 13 CUC cases (online supplemental table S1), thrombocytopaenia was detected in 11 cases, granulocytopaenia in eight cases and elevated C-reactive protein levels in seven cases on the day of onset. Cultures of cerebrospinal fluid were all negative. There was no sign of bone and joint infection, fungal endophthalmitis, renal infection, carditis or involvement of other end organs. All of the isolated strains were sensitive to amphotericin B, fluconazole, F-5 fluorine cytosine, voriconazole and itraconazole.

A peripherally inserted central catheter was removed after onset of the disease. Fluconazole was administered intravenously at a therapeutic dose of 8–10 mg/kg/day until the clinical symptoms of infection disappeared and two consecutive negative blood cultures were obtained at an interval of 1 week. The mean duration of anti-infective therapy was 24 days (range 18–31), including four cases receiving normal saline or plasma volume expansion therapy and three cases receiving vasoactive drugs. All the patients recovered from CUC after fluconazole treatment.

There have been rare reports about human CUC pathologies. A few available reports of CUC infection were in old people (68–88 years) and children (0–5 years), and treatments with flucytosine, fluconazole, liposomal amphotericin B or caspofungin improved the patients' condition.[5]

Candida spp, especially *C. albicans*, are more likely to be complicated by involvement of the end organs such as the brain, heart, kidney, eye and skeleton (online supplemental table S2)[6] while, in the CUC cases in our study, no fungal endophthalmitis, renal infection, carditis, bone and joint infection or involvement of other end organs was observed. A G test was performed in seven patients and the level was elevated in only three cases,

Table 1 Perinatal history and general information of the infants

Characteristics or risk factors	Mean (SD) or n
General characteristics	
Mother	
Mother age, years	33.85 (4.06)
Mode of delivery	
Caesarean delivery	3
Vaginal delivery	10
Antenatal glucocorticoids (Yes)	7
PROM	1
GDM	1
GH	5
Colpitis	1
Infant	
Gestational age, weeks	29.85 (1.14)
Birth weight, g	1329.23 (409.05)
Sex (male)	6
Twins (Yes)	4
Apagar score (1 min)	8.08 (2.40)
Apagar score (5 min)	8.85 (1.41)
Prophylactic vaccination	0 (0.00)
Major diagnosis at admission	
RDS	11
PDA	9
Asphyxia	3
Metabolic acidosis	9
NEC	1
IVH	4
Hyperbilirubinaemia	2
Pneumonia	2
Duration of parenteral nutrition, days	38.15 (16.50)
PICC	6
Postnatal corticosteroid exposure	4
Tracheal intubation	9
Prophylaxis of fluconazole	4
Antibiotic exposure in 3 days before infection	
Piperacillin	2
Imipenem	7
Meropenem	1
Sulperazone	1
Vancomycin	1

Drug sensitivity testing was performed using the Kirby-Bauer (K-B) method. Fungal sensitivity testing was performed in accordance with ROSCO (Denmark).
GDM, gestational diabetes mellitus; GH, gestational hypertension; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PICC, peripherally inserted central catheter; PROM, premature rupture of membranes; RDS, respiratory distress syndrome.

Table 2 Clinical characteristics of the infants

Clinical characteristics	Mean (SD) or n
Age at onset, days	15.85 (11.89)
Fever	2
Poor response	9
SaO_2 instability	11
Apnoea	7
Jaundice	5
Abdominal distension	4
Poor peripheral perfusion	3

suggesting that a negative G test result does not mean the absence of CUC.

Our study reported clinical characteristics, treatment and prognosis of CUC in 13 infants. The infection was controlled successfully in all cases after intravenous administration of fluconazole. It is noteworthy that, in the three infants infected with CUC reported by Lukić-Grlić *et al*,[7] one responded well to amphotericin B and the other two failed to respond to fluconazole and were later cured after replacement with amphotericin B and caspofungin, respectively. It was suggested that fluconazole could be used as the initial choice and, if it does not work effectively, it should be replaced by amphotericin B or echinocandins.

Contributors ZF conceived and designed the study. QL and LZ integrated and analysed data. QL and LZ drafted the original manuscript. SZ collected the clinical data. ZF edited the manuscript. All authors had full access to and verified the data. All the authors had final responsibility for the decision to submit the manuscript.

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1. Materials and Methods

1.1 Diagnosis criteria for CUC

The diagnosis criteria for CUC were: 1) the presence of clinical symptoms of neonatal infection: apnoea, or tachypnoea with retractions, nasal flaring, grunting, or tachycardia, or temperature instability; 2) positive result of C. utilis in two blood cultures from different sites at the same time by using VITEK2 COMPACT (BioMérieux, China).

2. Table S1

Table S1. Clinical and laboratory examination of 13 cases of CUC

Case No.	Neutrophilic granulocyte count (10^9/L)	Platelet count (10^9/L)	CRP (mg/L)	(1,3)-beta-D-glucan,G test (pg/mL)	CSF cell counts ($\times10^6$/L)	CSF protein level(g/L)	CSF Glucose level (mmol/L)	CSF culture	Routine urine test	ROP screen
1	5.9	223	24	10	4	1.16	2.91	Neg	N	Neg
2	3.3	92	6	ND	11	1.42	2.35	Neg	N	Zone 2,stage 2, plus(-)
3	.8	34	34	10	14	0.79	1.1	Neg	N	Neg
4	1.0	27	4	618	11	0.65	2.88	Neg	N	Neg
5	.8	30	17	ND	ND	ND	ND	ND	N	Zone 2,stage 3, plus(+)
6	.8	79	6	1098	17	1.08	1.61	Neg	N	Neg
7	.8	26	9	ND	8	1.56	1.76	Neg	N	Neg
8	6.5	50	17	ND	39	2.82	0.43	Neg	N	Neg
9	.8	81	1	10	ND	ND	ND	ND	N	Neg
10	14	126	16	ND	ND	ND	ND	ND	N	Neg
11	.1	28	6	ND	15	1.51	2.95	Neg	N	Neg
12	1.9	60	8	1000	ND	ND	ND	ND	N	Neg
13	1.0	75	4	10	29	1.41	1.9	Neg	N	Zone 1,stage 2, plus(+)

ND: Not done; N: normal; Neg: negative; Thrombocytopenia was defined as the platelet count <100×109/L in complete blood count (CBC); Granulocytopinia was defined as granulocyte count <1×109/L in CBC; and elevated C reactive protein (CRP) was defined as >8mg/dL.

28 **Table S2. Differences in clinical characteristics between Candida albicans and Candida utilis infection**

	***Candida albicans*[3]**	***Candida utilis candidemia***
Route of infection	Skin, Gastrointestinal tract, Vertical transmission, Blood	Blood,[1,2]Hospital acquired infection,[2]
Infection site	CNS, Heart, Kidney, Eye, Liver Spleen	Skin, Blood[1]
Clinical presentation	Late-onset spesis, Lethargy, Anpnoea, Cardiorespiratory failure	Poor response, SaO2 instability, Anpnoea, Respiratory Distress, Poor feeding,[1] Hypothermic,[1] Convulsions,[1]
Laboratory examination	Leukocytosis or leukopenia, Thrombocytopenia, Hyperglycaemia, CRP↑、PCT↑, (1,3)-β-d-glucan (BDG)↑, Blood culture positive,	Thrombocytopenia,[1] Granulocytopinia, CRP↑, (1,3)-β-d-glucan (BDG)↑, Blood culture positive,[1,2]

Risk factors	Lower gestational age, Lower birth weight, Vaginal delivery, Hospitalization for >7 days, Disseminated intravascular coagulopathy, Thrombocytopenia, Central venous catheterization, Broad-spectrum antibiotics, Invasive mechanical ventilation, Antacids (including H2 blockers), Systemic steroids, Candida colonization, Parenteral nutrition, Intravenous lipid emulsion, Groin catheters	Lower gestational age,[1,2] Invasive mechanical ventilation,[2] Central venous catheterization,[1,2] Surgical intervention (e.g. abdominal surgery),[2] Prophylactic antibiotics given[2]

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