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Pattern of Resistant Candida Infection: Case Series

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Abstract

Background: Neonatal candidiasis is one of the common nosocomial infections in the neonatal units especially in the extremely low birth weight (ELBW) infants due to many factors mainly the intensive interventional care. Some of the cases can become resistant to the common antifungal treatment and therefore you have to change the treatment and minimize interventions.

Objectives: To study the pattern of resistant invasive Candida infections in a neonatal unit and to assess whether minimal intervention in very low birth weight (VLBW) and extremely low birth weight babies contributes to clearance of infection.

Methods: Cases of very low birth weight and extremely low birth weight, who had persistent invasive Candida infection and were extensively treated and fully investigated in a neonatal unit at Maternity Hospital in Kuwait, were prospectively followed-up for over two years. Risk factors leading to Candida infection and its persistence were assessed.

Results: All of the six cases with persistent Candida infection cleared their infection only after they were transferred from intensive care unit to the special care baby unit with minimal invasive intervention. Conclusion: This study showed that minimal interventions in very low birth weight and extremely low birth weight neonates can lead to improved outcome by reducing number of risk factors that are associated with invasive Candida infection or with its persistence.

Keywords: Candidiasis; Preterm; Invasive; Interventions

Introduction

The reported incidence of Candida infection among VLBW neonates ranges from 2.6% to 12.9%. Most fungal infections in neonates were caused by *C. albicans*, followed by *C. parapsilosis*. However, there are recent reports of *C. glabrata* infections presumably associated with increasing use of fluconazole [1]. A number of risk factors have been identified that contribute to the occurrence of Candida infections, commonly, the frequent use of broad spectrum antibiotics, invasive and surgical interventions and use of total parenteral nutrition, besides presence of endotracheal colonization with Candida organism [1-5]. Therefore, it is reasonable to infer that by minimizing exposure of the very low and extremely low birth weight infants to neonatal unit interventions can reduce the chance of acquiring Candida infection and shorten the infection period.

The Neonatal Unit at Maternity hospital in Kuwait is considered as one of the largest units in the world accommodating around 30 intensive care beds, 20 intermediate care beds and 80 special care beds. It covers an annual 13 thousands deliveries in the hospital and receiving outborns from private sectors adding to the inborn coverage of around 7 thousands deliveries per year. The unit is almost continuously in full capacity and the rate of the total infection is high reaching up to 15%.

Our rate of Candida infection ranged from 4 to 8.4% according to two studies done in the unit [6,7]. Among the risk factors identified in these studies were longer duration of endotracheal intubation and total parenteral nutrition and more episodes of concomitant bacterial infection [6,7]. Here, we report a series of six cases who had persistent Candida infection in spite of adequate antifungal coverage. However, removal of some of the risk factors and ruling out other possible sources, such as colonization or vegetation appear to have contributed to clearance of infection.

Patients and Methods

Over 18 months from October 2011 till April 2013, we collected six cases of persistent Candida infection in the neonatal intensive care unit at Maternity Hospital, Kuwait. The cases were prospectively followed-up for over a two-year period. Risk factors leading to Candida infection and its persistence were assessed (Table 1). The data on antifungal susceptibility of Candida isolates as determined by Etest is provided (Table 2). The clinical history of each case is presented and discussed below:

Case 1

A baby boy who was born at 24 weeks gestation to a healthy 31-year-old mother. The birth was by spontaneous vaginal delivery after premature labor, and the rupture of the membrane occurred about 18 hours before delivery. The birth weight was 890 gm. The Apgar scores

were 6 and 7 at one and five minutes, respectively. The baby developed respiratory distress syndrome (RDS) for which he was ventilated, including C-PAP, for around 55 days. He was successfully extubated after short course of systemic steroids. He had a patent ductus arteriosus which closed spontaneously. The head ultrasound showed grade II intraventricular hemorrhage complicated by cystic changes.

	Cases					
	1	**2**	**3**	**4**	**5**	**6**
Gestational age in weeks	24	27	29	28	27	26
Birth weight (grams)	890	850	1210	1215	1040	835
Mode of delivery	SVD	ELSCS	SVD	SVD	ELSCS	SVD
Duration of ventilation in days	55	40	16	45	48	35
Duration of UVC and /or UAC in days	7	3	8	5	7	15
Number of central lines Inserted	2	P	1	1	1	1
Age of central lines removal	48		34	11	15	25
Duration of TPN in days	50	48	32	47	60	70
Number of antibiotics courses	3	2	2	3	4	3
Age if acquiring Candida in days	6	15	14	11	20	25
Age of Candida clearance in days	54	50	30	45	35	68
Number of antifungal drugs used	4	4	3	3	5	5

Abbreviations: SVD: Spontaneous Vaginal Delivery; ELSCS: Emergency Lower Segment Cesarean Section; UVC: Umbilical Venous Catheter; UAC: Umbilical Artery Catheter;
P: Peripheral Line; TPN: Total Parentral Nutrition

Table 1: Summary of demographic and clinical data of the six cases with candidemia.

Cases	**Candida sp.**	**Antifungal susceptibility (µg/ml)**			
		Fluconazole	**Voriconazole**	**Amphotericin B**	**Caspofungin**
1	*C. albicans*	0.38	0.008	0.047	0.023
2	*C. parapsilosis*	0.5	0.003	0.008	0.125
3	*C. albicans*	0.38	0.012	0.012	0.094
4	*C. albicans*	0.38	0.012	0.032	0.125
5	*C. parapsilosis*	0.38	N/A	0.064	0.38
6	*C. parapsilosis*	0.38	N/A	0.032	0.38

Table 2: Antifungal susceptibilities of Candida spp. isolated from the cases of candidemia as determined by Etest.

Baby was started immediately after birth on first line antibiotics: ampicillin and amikacin. But at 6 days of life the baby became sick and blood culture grew Candida albicans after 29 hours of incubation. Baby's respiratory condition deteriorated, requiring higher ventilatory parameters, and had progressive abdominal distension which was managed as stage one necrotizing enterocolitis. The blood culture showed growth of Enterobacter which was treated by tazocin and then meropenem. The candidemia was initially treated with amphotericin B, but replaced 5 days later by AmBisome due to persistence of *C. albicans* in the blood culture. Fluconazole was then added, however, the repeat blood culture after this combination therapy was still growing *C. albicans*, hence fluconazole was stopped and caspofungin was added to the AmBisome. At 44 days of age, the blood culture continued to be positive for *C. albicans* in spite of an improvement in baby's general condition, hence voriconazole was added to caspofungin while AmBisome was stopped. During the whole period of continuing growth of the *C. albicans* in the blood, the doses of the antifungal drugs were increased to 5 mg/kg, but without any benefit, and the baby had full and repeated investigation for any fungal vegetations that included ultrasound of kidneys, retinal examination, echocardiography and bone scan, all the investigations were negative. The central lines were also removed. Baby had also developed secondary nosocomial infections with methicillin resistant *Staphylococcus epidermidis*, gram negative Enterobacter and Enterococcus, and all were treated successfully, while the blood cultures continued to yield *C. albicans*. The immunological parameters were within normal range, whereas virological investigations showed IgM antibodies for parvovirus.

In the meantime, the baby developed total parenteral nutrition (TPN) related cholestasis and was started on feeds while in the intensive care isolation unit, which were progressively built up. Baby was then transferred to the special care baby unit for further care and cutting down the total parenteral nutrition and increasing the feeds.

The baby was without any interventions apart from the intravenous antifungal caspofungin. Repeated blood cultures sent thereafter became negative for *C. albicans*. Baby was discharged in good general condition and for prematurity follow up.

Case 2

A baby girl who was born to a 34-year-old primigravida mother at 27 weeks of gestation by emergency cesarean section because of pregnancy induced hypertension and prematurity. At birth, the baby weighed 850 grams with Apgar scores of 7 and 9 at one and five minutes, respectively. The baby had mild RDS for which she received ventilation and surfactant treatment and was extubated after three days. However, the baby developed frequent apneas and desaturation and had been kept on nasal continuous positive airway pressure (CPAP) alternating with mechanical ventilation. Baby was investigated, as infection was suspected, and the initial empirical antibiotics were changed to meropenem. Candida prophylaxis with fluconazole was started.

On the 14th day of life, the blood culture came positive for *C. parapsilosis*, which continued to grow for the whole 35 days in spite of changing different antifungals from fluconazole to amphotericin B to AmBisome and caspofungin and with adjustment of their doses. Drugs were used in different combinations, but the yeast still continued to grow from blood cultures. The baby had no concomitant bacterial infection. However, the baby had signs of disseminated intravascular coagulopathy with severe thrombocytopenia and neutropenia. She was fully screened for any Candida vegetations with negative findings. As the baby was off ventilator, she was transferred to the special care baby unit with instructions of minimal handling and invasive interventions. The blood cultures sent thereafter came as negative for any Candida growth.

Case 3

A baby boy, part of twin, born at 29 weeks gestation by spontaneous vaginal delivery to a 37-year-old primigravida mother, who had pregnancy induced hypertension but with no other risk factors. At birth, the baby weighed 1210 grams and had symptoms mild RDS for which he received one dose of surfactant and was mechanically ventilated for 20 hours. Baby did well for 13 days but then a developed signs of sepsis and respiratory distress, hence was re-intubated and ventilated mechanically for another 15 days. The blood culture at that time yielded *C. albicans* and which continued to remain positive in spite of changing and adding antifungal agents (Table 3). Initially, he was started on amphotericin B, then fluconazole was added, and later fluconazole was replaced by caspofungin on 15th day of the infection as per the advice of clinical microbiologist in our hospital, but the baby had persistently positive cultures for *C. albicans*. As the baby did not require mechanical ventilation he was shifted to special care unit and minimal intervention and handling was advised. The culture became negative after 10 days of removal of the all invasive interventions. He did not have evidence of bacterial sepsis but still had two courses of antibiotics, the initial ampicillin and amikacin and later empirical tazocin for the suspicion of secondary bacterial infection and necrotizing enterocolitis. Baby was investigated for any Candida colonization or vegetations, which proved to be negative. The other twin had minimal ventilation and invasive intervention and did not have the infection.

Cases	Antifungal agents				
	Fluconazole	Voriconazole	Amphotericin B	Caspofungin	5FC
1	5	21	38	30	NU
2	9	NU	28	28	NU
3	11	NU	35	28	NU
4	3	NU	21	25	NU
5	10	NU	45	NU	14
6	16	NU	30	25	21
Abbreviations: 5FC: 5 Flucytosine; NU: Not Used.					

Table 3: Duration (in days) of the anti-fungal treatment.

Case 4

28 weeks gestation baby boy who was delivered by spontaneous vaginal delivery and part of twins. He had RDS for which he was ventilated and given surfactant therapy, to be extubated on the 15th day of life and transferred to the special care baby unit. There, he was still on TPN and got sick with lethargy and frequent apneas a week later, and hence meropenem was started as gram negative infection was suspected, but later proved to have *C. albicans* infection in the blood on 33rd-day of his life. Unfortunately, the culture of the catheter tip of the long peripheral line on the 11th day of life yielded Candida sp. which had passed unnoticed. Cerebrospinal fluid (CSF) and urine culture were free from Candida sp. while the rectal and skin swabs became positive. Amphotericin was started first which was continued for 21 days, and fluconazole was added 3 days later. Three days later fluconazole was discontinued and caspofungin was added to the amphotericin which was continued for 14 days. The *C. albicans* infection persisted and the baby was investigated for the source of vegetation or extensive colonization which included the echocardiogram, ultrasound head and abdomen and retinal examination, and all proved to be negative. The baby remained stable in spite of infection with *C. albicans*, although the platelet count remained low although bleeding was observed. The baby was transferred to the special care baby unit on the 45th day of life and was

without TPN and other intervention. He was on full oral feed. On the 56th day of age, the blood culture became negative for the *C. albicans*.

Case 5

A baby boy, born at 27-week of gestation and as 2nd twin by emergency cesarean section. At birth, he had good Apgar score and weighed 1040 gm. He developed RDS and treated by mechanical ventilation and received three doses of surfactant. He had patent ductus arteriosus, which was treated and closed by two courses of Ibuprofen, and echocardiogram showed also ventricular septal defect. No surrounding vegetation was observed. . The baby had grade I intraventricular hemorrhage but no Candida ball. The baby had multiple courses of antibiotics: *Staphylococcus epidermidis* infection was treated with vancomycin, a course of tazocin was given for suspected necrotizing enterocolitis and one course of antibiotics was given for suspected late infection. He had positive blood culture for Candida parapsilosis. Cultures of long line catheter tip and urine also yielded *C. parapsilosis*, while the CSF culture was negative. This infection continued for 36 days despite treatment with multiple antifungal drugs, to be cleared only by the use of combination therapy with of Abelcet (lipid formulation of amphotericin B) and 5-flucytosine on 57th day of his age, but coincided with transfer to special baby care unit on 54th day of age, when he was free from interventions and was on full feed.

Case 6

Baby girl was born at 26 weeks gestation by spontaneous vaginal delivery to a primigravida mother, who had antepartum fever and leukocytosis for which she received antibiotics. The baby's birth weight was 835 gm, and had the intensive care of ventilation and surfactant therapy for RDS. She had the first line antibiotics for 7 days followed immediately by tazocine for suspicion of necrotizing enterocolitis for 14 days. At 25 days of age the blood culture grew Candida parapsilosis and continued to grow it for the next 46 days in spite of the use of different antifungals starting with amphotericin, which was combined with fluconazole after 5 days. The amphotericin was continued but the fluconazole was replaced with caspofungin 16 days later. On the 20th day of the diagnosis of the Candida infection, the amphotericin was replaced by Abelcet and caspofungin was continued. Flucytosine was added to replace caspofungin 5 days later. In spite of all these changes, the blood continued top yield *C. parapsilosis*. At 30th day of the diagnosis, Abelcet was again replaced by the caspofungin and the dose of the flucytosine was increased without benefit.

The baby was thoroughly evaluated for any hidden focus of Candida infection. However, on 33rd day of the diagnosis, Candida vegetation was detected on the kidneys by the abdominal ultrasound. The baby was ventilated for 46 days, and had the umbilical and central lines removed after the diagnosis of Candida infection. She was started on feeds on 60 days of age and then shifted to the special care baby unit on the 66 days of her age. There, she became on full feeds after 5 days of transfer and 3 days later the blood culture became negative for Candida. During the infection, the baby had thrombocytopenia which showed gradual improvement. During this period, she received another course of antibiotics, vancomycin for *Staphylococcus epidermidis* infection.

Discussion

We reported six cases of persistent candidemia in preterm babies that were cleared only after their transfer from the intensive care unit to the special care baby unit where there was no active intervention, all the central lines were removed and total parenteral nutrition was stopped.

In all the six cases, a number of antifungal drugs were used either separately or in combination to eradicate the infection [3,8], but without success. The Case 1 and Case 6 were the most difficult ones and had the most of the risk factors and also had the refractory infection for the longest period. In our unit, we use prophylactic fluconazole only in the extremely low birth weight babies, and hence it was used in Case 1 and Case 2, but still they got the infection. In all the six cases, Candida organisms were susceptible to all the antifungal drugs *in vitro* but infection persisted despite appropriate therapy. We are following the dosing system written in the Neofax, a neonatal dosage booklet by Young and Mangum. Our standard of Candida treatment is to start with intravenous fluconazole prophylaxis from day 7 of life, use oral mycostatin in colonized babies, and start with amphotericin B with any proved or highly suspected infection [9,10]. However, for the resistant infection, we do not have a fixed protocol, we go by the discretion of the consultant neonatologist on service and with the help of the microbiologist.

Wade et al. and Nakamura et al. stressed on the proper dosing of the antifungals for the best response [11,12]. We took care of the appropriate doses of the antifungal drugs, usually starting with the maximum dose, the second antifungal was added only if cultures for Candida sp. remained positive or if there was an indication for a replacement due to specific organ dysfunction/toxicity, such as renal function deterioration. Kawaguchi et al. reported one of the newer echinocandins, micafungin for the resistant Candida infections, which is not available in our unit, hence we have limited choice of antifungals, mostly limited to the use of fluconazole, amphotericin B or its lipid formulations (AmBisome or Abelcet), and caspofungin [13]. Recently, we had access to 5-flucytosine, which we used in two cases (Case 5 and Case 6) but without much success.

Most of the previous reports stressed on the elimination of the risk factors to prevent and control of the existing Candida infection in the very and extremely low birth weight babies [1-8,12-15]. In our cases, these measures were introduced appropriately, but still the infection persisted and cleared only after adopting strategy of minimal handling and invasive intervention, which was only achievable in the quite special care baby unit and away from the neonatal intensive care, and in this context the present report is noteworthy.

The rate of candidemia in our unit has been high in spite of the fact that almost all the Candida spp. isolated from the patients were susceptible to antifungal agents used for therapy. None of our three cases with persistent candidemia had vegetation or any hidden focus of infection. The reasons for persistence of candidemia are not known. However, it is possible that gradual maturity of immune system as the infants age may play a crucial role in eliminating the fungus even though they were treated with fungistatic and/or fungicidal drugs.

Overuse of broad spectrum antibiotics, active invasive intervention, surgical procedures and prolonged use of total parenteral nutrition have been implicated in the onset of candidemia. We unfortunately still use meropenem (carbapenem) for the gram negative infections which are one of the risk factors predisposing for Candida in the preterm babies [10,15]. Five of our babies, Cases 1, 2, 4, 5 and 6 were

started on meropenem for suspicion of infection, but cephalosporins are not used in our unit as per our antibiotic policy. Our rate of coagulase negative Staphylococcus infections remains to be high, and hence there is increased use of vancomycin. Benjamin et.al. reported increased incidence of Candida infections in unit with overuse of carbapenem and cephalosporin [10]. We use short courses of postnatal steroids for the treatment of bronchopulmonary dysplasia and we stop infusing intralipid emulsions once the diagnosis of systemic candidiasis is proved. Many previous studies have reported the benefit of minimizing invasive intervention for reducing/eradicating the occurrence of gram positive and gram negative bacterial infections. However, this seems to be the first report, where a similar strategy was successfully adapted to eradicate/clear persistent Candida infection.

One of the limitations of this study is a case series and would be helpful if it is a controlled study. However, since it is still small number of patients collected, we thought to report the cases first and then when the number is increasing then we look forward to do the case-control study. In fact this is our goal for the next study, but we thought we should publish this observation of the six babies. We have recently encountered more cases of the same problem but after we have sent this manuscript. We will add this comment in the discussion as a limitation of the study.

Conclusion

Candida infection poses a therapeutic challenge in the neonatal units mostly for the low and extremely low birth weight infants. We showed that by minimizing invasive intervention and increasing enteral feeding can contribute to recovery from persistent Candida infection.

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