Pattern of Candidiasis in the Newborn: A Study from Kuwait

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Key Words

Candidiasis · Low birth weight · Risk factors · Laboratory diagnosis · Buffy coats

Abstract

Objectives: To determine the rate and pattern of *Candida* infection in a large neonatal unit in Kuwait. **Methods:** A prospective study of all newborn infants who were admitted to the neonatal intensive care unit (NICU) at Maternity Hospital in Kuwait during the year of 1997 and who were suspected of having *Candida* infection were collected and analyzed. Method of selection of neonates, laboratory parameters and possible risk factors of the infection were identified and defined. **Results:** *Candida* infection was recognized in 22 (8.4%) cases out of 263 total infants admitted to the NICU. All the proven cases originated from 168 infants of birth weight less than 2,000 g with an incidence of 13%. In addition, *Candida* infection was suspected and treated without positive culture in 15 infants (5.7%). Cases with proven *Candida* sepsis had lon-

ger mean duration of endotracheal intubation ($p < 0.03$) and total parenteral nutrition ($p < 0.03$) and more episodes of concomitant bacterial infection ($p < 0.01$) compared to infants with suspected candidiasis. **Conclusion:** For an early diagnosis of candidiasis, a high index of suspicion in septic low-birth weight infants is always warranted since the clinical and laboratory diagnostic parameters are difficult to differentiate between suspected and proven cases.

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Introduction

Neonatal candidiasis, one of the common nosocomial infections in most neonatal units, reaches up to 20%, especially in the extremely premature infants [1–11]. Several factors are believed to contribute to its occurrence, most commonly prematurity and antibiotic overuse [2, 3, 5, 8, 11, 12]. In addition, other factors may play a role in predisposing to the infection such as use of total parenteral nutri-

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tion, intravenous additives, use of central lines particularly for long duration, prolonged endotracheal intubation and the use of drugs such as theophylline [2, 3, 6, 8, 12–15]. There are clinical, hematological and biochemical parameters by which *Candida* infection is suspected and treatment is therefore initiated since blood cultures are not always positive [11, 15–17]. Mortality rate from *Candida* infection varies from 10 to 55% in extremely premature babies; there are no studies to define the long-term outcome in the survivors [9, 14, 17–19].

The neonatal intensive care unit (NICU) at Maternity Hospital in Kuwait is one of the largest in the country with a high rate of infection reaching up to 27%. The pattern of *Candida* infection in our low-birth weight neonates remains unclear. Therefore, the aim of this study was to define the pattern of *Candida* infection in our NICU and to determine the method of treating the suspected infection.

Materials and Methods

Sample Selection

All infants admitted to the NICU at Maternity Hospital in Kuwait during the period from January 1st to December 31st 1997 who were suspected of having systemic candidiasis were prospectively studied. This was based on clinical signs of reemergence of respiratory distress or apnea, abdominal distension, poor activity and lethargy and on the presence of at least one hematological and/or biochemical parameter. These parameters included sudden increase in the total white cell count or drop in the total count to below 5,000, abnormal immature-to-total white cell count ratio, thrombocytopenia, high C-reactive protein, fluctuating blood sugar, electrolyte disturbance and unexplained metabolic acidosis. In addition, positive surface cultures for *Candida* including skin, rectal swab, endotracheal and upper gastrointestinal aspirates were considered as cases of systemic candidiasis in the presence of clinical or laboratory signs. Intravenous amphotericin B was then used to treat these infants after screening them for deep-seated infections through tak-

ing blood, suprapubic urine and cerebrospinal fluid, and documenting results of cultures of the tip of central intravenous and other deep-seated catheters. These infants were then divided into two groups: (1) those with proven candidiasis documented by positive culture of the deep sites, and (2) those with suspected infection with negative deep cultures including those with positive surface cultures and those with abnormal biochemical or hematological parameters.

Comparison of the two groups was done in terms of risk factors and the presence of clinical, hematological and biochemical parameters. The risk factors chosen were the duration and type of antibiotics used at least 72 h prior to the start of amphotericin B, duration of the endotracheal intubation, the central intravenous catheterization and other deep-seated lines such as thoracotomy tubes or peritoneal catheters. Moreover, use of drugs such as dexamethasone, theophylline, H₂ receptor antagonists, cisapride and indomethacin 72 h prior to commencement of amphotericin B was also chosen as risk factors, in addition to use of total parenteral nutrition and blood products. Chest X-ray and ultrasound of the kidneys and fundal examination using indirect ophthalmoscope were other methods of screening for *Candida* infection.

Microbiological Screening and Management

Isolation of *Candida* or finding any evidence of candidiasis was accomplished by culture and by buffy coat smear examination of the blood or finding *Candida* antigen in the blood. Blood cultures were processed by lysis centrifugation technique (Isolation System, Wampole Laboratories, N.J., USA). In addition, blood samples drawn in sterile tubes containing EDTA (Vacutainer, Becton-Dickinson, USA) were centrifuged at 3.5×10^3 rpm for 5 min. The buffy coats were removed with a sterile Pasteur pipette for microscopic examination by Gram stain and culture. All the cultures were made on Sabouraud glucose agar and/or blood agar. Yeast isolates were identified as *Candida albicans* by positive germ-tube test.

The *Candida* antigen, a heat-labile glycoprotein, was detected by a commercially available Cand-Tec latex agglutination system (Ramco Laboratories, Inc., Houston, Tex., USA). No molecular typing of the organism was done to locate the source of infection. Amphotericin B was started on the infant once the infection was suspected at a dose of 0.5 mg/kg/day by 30-min infusion and 5-flucytosine was added in *Candida* meningitis. Death from *Candida* infection was calculated as an outcome measure.

Table 1. Characteristics of infants included in the categories of proven and suspected *Candida* infection

	Proven candidiasis (n = 22)	Suspected infection (n = 15)	p value
Mean birth weight, g	1,030 ± 350	855 ± 122	0.04
Mean gestational age, weeks	29.3 ± 2.9	28.3 ± 1.6	NS
Sex (male:female)	8:14	7:8	NS
Respiratory distress and/or apnea	20 (90.9%)	15 (100%)	NS
Evidence of necrotizing enterocolitis	2 (9.1%)	5 (33.3%)	
Disseminated intravascular coagulation	3 (13.6%)	5 (33.3%)	
Blood sugar fluctuation	15 (68.2%)	13 (86.7%)	NS
Electrolyte disturbance	10 (45.5%)	9 (60%)	NS
Metabolic acidosis	9 (40.9%)	9 (60%)	NS
Mean total white cell count at diagnosis	29.4 ± 9.4	21.8 ± 7.3	0.014
Thrombocytopenia (count <100,000)	19 (86.4%)	12 (80%)	NS
High C-reactive protein	18 (81.8%)	12 (80%)	NS
Chest X-ray suggestive of <i>Candida</i> pneumonia	4 (18.2%)	1 (6.7%)	
Evidence of <i>Candida</i> on fundus examination	1	1	
Treatment with 5-flucytosine	5 (22.7%)	2 (13.3%)	NS
Mortality	5 (22.7%)	4 (26.7%)	NS

Table 2. Possible risk factors associated with the development of candidiasis

	Proven candidiasis (n = 22)	Suspected infection (n = 15)	p value
Mean duration of antibiotics, days	6 ± 3.3	6.1 ± 3.7	NS
Mean duration of central venous lines, days	9.9 ± 8.7	10.3 ± 6.8	NS
Mean duration of endotracheal intubation, days	18.5 ± 9.6	11.6 ± 6.6	0.02
Mean duration of total parenteral nutrition, days	15.8 ± 8.6	8.0 ± 1.1	0.003
Use of dexamethasone	7 (31.8%)	2 (13.3%)	NS
Use of H ₂ receptor antagonists	9 (40.1%)	9 (60%)	NS
Use of cisapride	10 (45.5%)	8 (53.3%)	NS
Use of theophylline	22 (100%)	13 (86.7%)	NS
Use of indomethacin	9 (40.1%)	6 (40%)	NS
Use of blood products	9 (40.1%)	7 (46.7%)	NS
Undergoing surgery	1 (4.5%)	2 (13.3%)	
Presence of concomitant bacterial infection	12 (54.5%)	2 (13.3%)	0.01
Positive surface culture for <i>Candida</i>	3 (13.6%)	4 (26.7%)	NS

Fig. 1. Distribution of *Candida* cases (January to December 1997).

Statistical Analysis

The data were entered into an SSPS data-base program and statistical analysis was performed using the Student t test for continuous variables and the chi-square test for categorical variables to compare the suspected and the proven *Candida* infections.

Results

Study Population

Over the 1-year period, 263 newborn infants were admitted to the NICU. Out of these, 168 (63.9%) were below 2,000 g and 70 (26.6%) were below 1,000 g. *Candida* infection was suspected in 37 infants with a mean birth weight of 960 ± 290 g and a mean gestational age of 29 ± 2.5 weeks. There were 15 males and 22 females. There was no congenital candidiasis among these infants.

Candida Isolation

Candida infection was documented by positive deep-seated cultures in 22 cases, of

which 7 were due to *C. albicans* and 3 due to *Candida parapsilosis*. The remaining 12 non-*albicans* isolates were not speciated. Therefore, the overall rate of *Candida* infection in the unit was calculated to be 8.36% and for those with a low birth weight it was 13.1%. Fifteen infants had no proof of *Candida* by deep-seated cultures, but received full treatment. Buffy coat smear and *Candida* antigen were positive in 1 case in each group. There was a total of 7 cases in both groups that had a positive surface culture, i.e. *Candida* colonization, which gave a rate of 19% in the neonates admitted to our unit (table 2).

Group Characteristics

The characteristics of the infants in the two groups and the distribution of cases according to birth weight and gestational age are shown in table 1. Additional cases of candidiasis were seen in the months of January, April and May (fig. 1).

Among the risk factors documented, infants with proven *Candida* infection had significantly longer mean duration of endotracheal intubation ($p < 0.02$) and total parenteral nutrition ($p < 0.003$) and the presence of more concomitant bacterial infection 72 h prior to the start of antifungal treatment ($p < 0.01$) than those with nonproven candidiasis (table 2).

There were no difference between the two groups in the other risk factors chosen. Only 4 cases in the proven infection and 1 case in the suspected infection were not exposed to antibiotics 72 h prior to the start of amphotericin B. In the cases of proven *Candida* sepsis, 8 were exposed to cephalosporins, 4 to vancomycin, 1 to amikacin, and the rest to different types of antibiotics. In those cases with suspected *Candida* infection, 6 were exposed to cephalosporins, 2 to vancomycin and 7 to different types of antibiotics. There were 5 deaths (22.7%) in infants with proven candidiasis and 4 (26.7%) with suspected infection.

Discussion

Although our study was limited to a 1-year period, it reports a high overall incidence (8.4%) of *Candida* infection in our NICU. This may be attributed to the fact that 63.6% of our *Candida*-infected infants in the proven category had birth weights below 1,000 g. Consistent with our observation, the incidence of neonatal candidiasis has been reported to be inversely proportional to birth weight, and this itself is an important risk factor [20, 21]. Moreover, the crowded setting of our unit makes the possibility of cross-infection very high in spite of the precautions of hand washing and disinfection in the unit.

Our data showed that there were few differences in the characteristics of the patients

and in their clinical and laboratory parameters, and in the possible risk factors between those infants with proven candidiasis and those with suspected infection. This reinforces the view that a high index of suspicion may lead to the increased diagnosis of candidiasis in septic, very-low-birth weight infants.

Direct microscopic examination of buffy coat has been reported to be highly specific (100%) with 100% positive predictive value in the rapid diagnosis of candidemia [22]. However, sensitivity of the test is about 60% [22]. Our low positivity of buffy coat smears could be attributed either to insufficient quantity of blood samples examined or low fungemic load in some of our neonates. Perhaps use of Wintrobe's tube, where 0.5–1.0 ml of blood is sufficient to provide a good buffy coat smear, could have yielded more positive results. However, more extensive evaluation of this method in the rapid diagnosis of candidemia is warranted. Similarly, detection of *Candida* antigen by use of the Cand-Tec latex agglutination kit was not of much assistance in the diagnosis of candidiasis in our patients. The kit, which has been largely evaluated in adult *Candida* patients, has demonstrated low sensitivity [23]. To our knowledge, there are not many reports on the sensitivity of *Candida* antigen detection in the diagnosis of neonatal candidiasis. It may be stated here that the *Candida* antigen is not present continuously in the circulation, and frequent sampling may be necessary to improve sensitivity [21, 23, 24]. Moreover, the Cand-Tec latex agglutination kit used in the study may yield false negative results in patients with disseminated candidiasis due to *C. parapsilosis* and *Candida krusei* [23, 24].

Although we have not speciated the non-*albicans Candida* isolates, *C. parapsilosis* has emerged as an important pathogen associated with nosocomial candidiasis in premature neonates [25, 26]. Apart from very low birth

weight and reduced gestational age, other risk factors that contribute to the high risk of *Candida* sepsis in low-birth weight infants include prolonged hospitalization, instrumentation, central venous catheters, multiple antibiotic courses and hyperalimentation [26, 27]. A multivariate analysis of some of these factors suggests that infants with proven *Candida* infection had significantly larger mean duration of endotracheal intubation, total parenteral nutrition and greater frequency of concomitant bacterial infection. It is therefore important that effective clinical management should focus on minimizing exposure to these factors in high-risk neonates. *Candida* colonization by surface culture was demonstrated in 19% of our neonates, a finding that is comparable with previous reports [28, 29]. Our observations support the view that prior *Candida* colonization is not uncommon in very-low-birth weight infants and this represents an important risk factor.

A comprehensive epidemiologic study coupled with genotyping of the isolates origi-

nating from healthcare staff or other sources is required to assess the role of various factors contributing to the occurrence of candidiasis in our NICU. The mortality from *Candida* infection in this study (23%) is consistent with that reported in other studies, especially in infants with birth weights below 2,000 g [9, 14, 17, 18].

Conclusion

Candida infection remains one of the diagnostic challenges in our neonatal unit. Until more refined and sensitive laboratory diagnostic methods become available, *Candida* infection should be strongly suspected in a septic low-birth weight neonate who deteriorates despite antimicrobial antibiotic treatment, especially when recognizable predisposing factors are present.

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