Risk factors for Candida infections in a neonatal intensive care unit in Costa Rica

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Summary

Objective: To identify potential risk factors associated with Candida infections and compare these risk factors between patients who both died and survived.

Study design: A group of patients with positive Candida spp. blood cultures admitted to a neonatal intensive care unit (NICU) in Costa Rica between January 1994 and December 1998. Cases were identified through a computerized search of the microbiology laboratory’s database on blood cultures.

Results: One hundred and ten newborns were identified. Sixty-six patients (60%) were male; 46 (62%) were preterm infants. Thirty-seven (34%) patients died. Twenty (54%) of them died within three days of the candidemia diagnosis and 17 had disseminated Candida infection on autopsy. Candida albicans and Candida tropicalis were isolated in 90% and 10% of blood cultures, respectively. Mean ± SD (range) number of days from admission to NICU to the initial positive blood culture were 13.5 ± 8.5 (1—30) days. Most patients had at least two positive blood cultures (range 1—8). Median (range) days for the sterilization of blood culture were four (1—25) days. Significant differences in survival were identified in patients with axillary-inguinal lesions, apnea and seizures.


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Introduction

Since the early 1980s the survival rate of preterm infants has dramatically improved. However, this has resulted in the emergence of secondary infections such as those caused by Candida spp. This organism plays an important pathogenic role in neonatal intensive care units (NICU), and it represents the third most common cause of late-onset sepsis in NICU patients. More importantly, approximately 1–3% of these newborns have birth weights <1500 g. Candida species may be acquired vertically from the mother or after colonization in the NICUs. Although fungemia is the most common presentation, Candida spp. can disseminate and produce other types of infections, including meningitis; renal, splenic or hepatic abscesses; endophthalmitis, osteomyelitis or invasive dermatitis. The gross mortality of fungal infections in NICUs ranges from 25–50%. Furthermore, a delay in the recognition of Candida infections and the initiation of appropriate antifungal therapy often leads to significant morbidity and mortality rates among high-risk infants.

The objectives of this study were to identify potential risk factors associated with Candida infections in the NICU at the Costa Rican National Children’s Hospital and to compare these risk factors between patients who died and survived. These results may be used to elaborate guidelines to prevent these serious infections and improve their diagnosis and management.

Materials and methods

This was a retrospective study of patients who were admitted to the NICU and had a positive Candida blood culture. Cases were identified by reviewing the hospital’s records of laboratory cultures. NICU patients who had had candidemia between January 1994 and December 1998 were included in this study.

Definition of terms

Candidemia: the growth of Candida species from peripheral or central venous blood samples. It was considered contributory to mortality if death occurred within three days of a positive blood culture or if there was evidence of disseminated candidiasis in the autopsy.

Congenital candidiasis: neonatal candidiasis acquired during passage through an infected birth canal or in utero. Lesions appear after the first week of life, and commonly include thrush, perianal and diaper dermatitis.

Axillary-inguinal lesions: erythematos macules, papules and pustules overlying areas of confluent macular erythema distributed on axillary and/or inguinal areas.

Apnea: an abnormal respiratory pause of at least 20 seconds or associated with cyanosis, marked pallor, hypotonia or bradycardia.

Mucositis: inflammation of the mucous membranes lining the digestive tract from the mouth to the anus.

Abdominal distention: an increase in abdominal circumference, usually due to gas in the intestinal tract.

Fever: axillary temperature above 37.5 °C.

Bleeding: extravasation of blood or plasma from mucous membranes, organs or puncture sites.

Hypothermia: axillary temperature ≤36 °C.

Reference ranges used for blood values were:

- Thrombocytopenia: Less than 150 x 10^9/L
- Anemia: Hemoglobin less than 10 g/dL
- Leukocytosis: leukocytes more than 15 x 10^9/L
- Leukopenia: leukocytes less than 5 x 10^9/L
- Hyperglycemia: glucose more than 116 mg/dL
- Hypoglycemia: glucose less than 50 mg/dL

Medical records were reviewed to collect the following information: demographic characteristics, use of parenteral nutrition and antibiotics, number and duration of invasive procedures (such as surgery, endotracheal intubation and intravascular devices) and length of hospitalization.

Additional data included: age, onset of fungal infection, clinical signs and symptoms, laboratory tests, identification of the causative organism, antifungal therapy and complications.

Data were collected in standardized forms, entered and analysed with Epistat True 4.0 software. Categorical variables were compared using contingency 2 x 2 tables, by Chi-square and log-likelihood ratio; 95% confidence intervals were calculated. A p value of ≤0.05 was considered statistically significant.
One hundred and ten newborn patients who had a positive Candida blood culture were identified and analysed. Sixty percent (66/110) were male and 62% were premature infants. Thirty-four percent (37/110) died, 20 of whom (54%) died within three days of the diagnosis of fungemia.

Forty-six percent (17/37) of patients who died had evidence of disseminated fungal infection at autopsy, of whom seven (41%) died within three days of the Candida diagnosis. More importantly, Candida was a contributory factor to mortality in 29/37 (78%) patients. Of all the patients who died, seven had congenital candidiasis. Patients with congenital infection had an erythematous maculopapular or vesicular rash with or without pneumonia, and diagnosis was made as early as three days after birth (range 1–5 days).

Clinical manifestations associated with candidemia are presented in Table 1. Significant differences between those patients who survived and died were identified: axillary-inguinal lesions, apnea and seizures. The most common manifestations were: skin lesions, 66/110 (60%); mucositis, 63 (57%); abdominal distention, 63 (57%); cyanosis, 55 (50%) and fever, 50 (45%). Other manifestations included apnea, hypothermia, and skin rash.

Laboratory findings are shown in Table 2. There were no significant differences in any of these laboratory tests among infants who survived or died. Although only five patients had a cerebrospinal fluid (CSF) culture positive for C. albicans, many patients had one or more abnormal findings in the CSF as shown in Table 3.

*Candida albicans* accounted for 90% of the positive blood cultures and *C. tropicalis* accounted for the remaining 10%. Antifungal drug susceptibility testing was not performed. Forty-six percent (17/37) of newborns who died had a positive blood culture post-mortem.

Mean ± SD days between admission to the NICU and initial positive culture were 13.5 days (±4) (range 1–20 days). Seventy-five percent (82/110) of patients had at least two positive cultures during the course of infection. The median length for the sterilization of blood cultures was four days (range 1–25 days).

Table 4 shows the risk factors identified in these patients: previous use of antibiotics in 95%, endotracheal intubation for a mean of nine days in 64%, use of central devices including umbilical lines for a mean of eight days in 89%, and parenteral nutrition for a mean of 12 days in 84% of patients. Other risk factors identified were abdominal and thoracic surgery. Regarding risk factors, there were no signifi-
cant differences between those who survived and those who died.

All patients received amphotericin B 0.5 mg/kg during the first day and then 1 mg/kg for a mean ± SD of 17 days ([μ]7), (range 10—23 days). Fluconazole was used in combination with amphotericin B in 15/110 (14%) cases for a median of 12 days, (range 8—27 days); and 5-fluorocytosine plus amphotericin B in nine cases (8%), for a median of three days, (range 2—6 days). No adverse events were reported with any of these drugs. Additionally, no differences regarding outcome were identified between antifungal therapies.

Discussion

Newborns admitted to intensive care units are at greater risk of contracting nosocomial infections. These risks are associated with their susceptibility to infections as a result of both prematurity and invasive medical equipment needed for survival. Rates of Candida bloodstream infections have increased dramatically during the past decade, in part related to the improvement in survival rates of infants with very low birth weights.8

Other risk factors associated with candidiasis include immunocompromized hosts, early fungal gastrointestinal tract colonization, predisposition to invasive fungal dermatitis, and use of parenteral antibiotics and corticosteroids.9

In this study the following were identified as risk factors: use of broad-spectrum antibiotics, endotracheal intubation, use of central lines, parenteral nutrition and abdominal or thoracic surgery. No differences were identified between those patients who survived and those who died.

Previously it has been established that the type and number of antibiotics such as third generation cephalosporins,10 vancomycin11 or carbapenems12 can predispose to Candida infections, especially in immunocompromized hosts. The data here confirmed these reports. Use of multiple invasive devices, such as catheters and endotracheal tubes may be responsible for the nosocomial spread of pathogens through the hands of healthcare workers (HCW). Because this was a retrospective study, samples from potentially colonized HCW in the unit were not obtained. More importantly, during the period of this study, parenteral nutrition including lipids was given without the use of appropriate filters, contributing to a potentially important extrinsic mechanism of infection/contamination in this population. The hands of HCW and environmental surfaces are newly-appreciated potential reservoirs for nosocomial strains of Candida. More importantly, preventive measures such as the use of filters for parenteral nutrition, and a restrictive policy of antibiotic use to decrease Candida colonization/infection rates, should be implemented to reduce the morbidity and mortality associated with these infections.

Even though candidemia has been associated with prolonged hospitalization, most fatal cases occurred in neonates younger than three weeks of age.8,13,14 Given that infants of this age have decreased immunity, their host response to Candida may contribute to mortality.15,16

Candida albicans is the most common cause of candidemia. It may be vertically transmitted from

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Laboratory findings in CSF samples from newborns with candidemia.</th>
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<tbody>
<tr>
<td>Laboratory findings</td>
<td>Survived N = 73 (66%)**</td>
</tr>
<tr>
<td>Leukocytes (cells/mm³)*</td>
<td>10 ± 15 (0—25)</td>
</tr>
<tr>
<td>Protein (mg/dL)*</td>
<td>77 ± 68 (45—155)</td>
</tr>
<tr>
<td>Decreased glucose**</td>
<td>20 (54)</td>
</tr>
<tr>
<td>Positive culture</td>
<td>0</td>
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</tbody>
</table>

p > 0.5.

* Mean ± SD (range).

** Number of patients (%).

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Risk factor identified in newborns with candidemia.</th>
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<tbody>
<tr>
<td>Factor</td>
<td>Number of patients N (%)</td>
</tr>
<tr>
<td>Previous use of antibiotics</td>
<td>105 (95)</td>
</tr>
<tr>
<td>Central catheters</td>
<td>98 (89)</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>92 (84)</td>
</tr>
<tr>
<td>Tracheal intubation</td>
<td>70 (64)</td>
</tr>
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Other factors identified: abdominal surgery: 40 (35%); thoracic surgery: 39 (35%).
The potential for nosocomial infection from several Candida species, such as C. albicans, has been well studied. In this report 10% of patients had C. tropicalis candidemia, which may be acquired by horizontal transmission. Its ability to produce clusters has been one of its major pathogenic components. However, C. tropicalis has not been thoroughly studied and could potentially play an important role in nosocomial infections.20,21 Few patients had candidemia by species other than C. albicans; however, mortality was higher in newborns infected with C. albicans.

Even though Candida vaginitis occurs in 20–30% of pregnancies, it does not usually produce obstetric complications.22 This was an unexpected finding since mortality rates in congenital candidiasis have been lower in previous reports. In premature neonates weighing <1000 g, the risk of systemic fungal infection reported is 67% and mortality is 40%. This is in contrast to premature newborns weighing >1000 g where the risk of systemic infection and death is 10% and 8%, respectively.22,23 Moreover, invasive fungal dermatitis is a disease of the smallest and most immature neonates. This is usually associated with vaginal birth, steroid administration, and hyperglycemia.23 As with previous studies, it is believed that the skin serves as a portal of entry for colonizing fungal species and may lead to disseminated infection. Life-threatening disseminated candidiasis can occur, with death in the immediate neonatal period, as seen in this and previous reports.4 The mortality rate associated with these infections is 20–50% and occurs among all ages. In this report, the mortality rate was 34%.

Monotherapy with amphotericin B appeared to be effective in most cases.24,25 Occasionally a second antifungal agent may be needed for persistent candidemia, as occurred in 24 patients from this series. Most of the clinical characteristics of candidemia in this study were similar to previous publications. However, it was identified here that the finding of axillary and inguinal lesions, apnea and seizures were more common in those patients who died. Due to this new finding and the limitation of this type of study, future prospective case-control studies should be carried out to confirm this finding. Abnormal CSF findings also deserve further consideration. Diagnosis of fungal meningitis is important since it mandates adjustments in antifungal therapy. Many CSF samples had one or more cytologic or biochemical abnormalities, which might suggest that more patients had fungal intracranial involvement, despite negative CSF culture. Negative cultures in the presence of CSF abnormalities could reflect a partially treated fungal meningitis or may represent the inherent difficulties for this microorganism to grow from a small CSF sample, lower inoculum size or improper use of special isolation techniques.26,27

In conclusion, invasive candidiasis is frequent in NICUs, and it is associated with high mortality rates in premature newborns in Costa Rica. Ongoing epidemiological surveys have increased the understanding of reservoirs and modes of transmission of Candida spp. Continued surveillance is necessary to estimate the real incidence and impact of this infection.

Conflict of interest: No conflict of interest to declare.

References


