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Pediatrics 1984;73;138

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Systemic Candidiasis in Very Low-Birth-Weight Infants (<1,500 Grams)

Dana E. Johnson, MD, PhD, Theodore R. Thompson, MD, Thomas P. Green, MD, and Patricia Ferrieri, MD

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ABSTRACT. Previous reports in the literature have documented that systemic infection with Candida albicans in very premature infants is frequently fatal (54%) or associated with significant morbidity in survivors (25%). Five patients with a mean birth weight of 829 g had a diagnosis of systemic candidiasis during their stay in a newborn intensive care unit. All infants survived with minimal sequelae following aggressive early treatment with amphotericin B and 5-flucytosine. A review of these five extremely premature infants and 26 previously reported patients suggests the following: (1) disseminated candidiasis is common in the absence of positive findings in blood, CSF, and/or urine cultures; (2) transient candidemia rarely resolves without therapy; (3) meningitis and osteoarthritis occur more frequently than in older patients with disseminated disease; and (4) premature infants tolerate amphotericin B and 5-flucytosine well. Infants who are found to have systemic cultures positive for candidiasis should be treated by (1) removing all factors that predispose to systemic candidiasis (eg, indwelling catheters, broad-spectrum antibiotics); (2) early initiation of systemic antifungal therapy with amphotericin B and 5-flucytosine; and (3) searching for additional foci of disease. After the disease is recognized and treatment is prompt and aggressive, outcome can be substantially improved. Pediatrics 1984;73:138-143; Candida, low-birth-weight infants, sepsis, meningitis.

Systemic candidiasis in very premature infants (<1,500 g birth weight) is a serious infection associated with high morbidity and mortality. Little information is available, however, on the recognition and treatment of infants at risk for systemic disease, as no one has detailed the successful treatment of more than one infant. Therefore, it has been difficult to develop diagnostic criteria and to evaluate the type, duration, and complications of drug therapy in these infants. This report details the successful clinical management of five extremely premature infants with a mean birth weight of 869 g (28 weeks' gestation) who had a diagnosis of systemic Candida albicans septicemia while in our newborn intensive care unit. Data from these patients, plus a review of the literature, were used to develop suggestions for diagnosis and treatment of systemic candidiasis in very immature infants.

PATIENT POPULATION

The five patients (all female) included in the study were hospitalized in the Newborn Intensive Care Unit (NICU) at the University of Minnesota Hospitals during the time period from Oct 1, 1980, through April 1, 1982. Four of the five infants were cared for in our NICU during their entire postnatal course. Patient 4 was transferred to our NICU at 138 days of age with right-sided cardiac failure secondary to a right ventricular fungal mass. During this period of time, 166 infants with a birth weight <1,500 g were admitted to our NICU. The five patients represent a 3% incidence of systemic candidiasis in infants weighing <1,500 g at birth.

The clinical course, positive cultures for Candida albicans, and treatment for all five of our patients are shown in Table 1. The infants had severe apneic spells at the time of their original positive cultures. All infants had been treated with broad-spectrum antibiotics and had indwelling catheters in place for central parenteral nutrition prior to the documentation of Candida infection. Patients 2, 4, and 5 had additional factors that have been associated with systemic invasion by the organism. Patient 2, whose body surfaces were colonized with C albicans at birth, had an iatrogenic esophageal perforation.
shortly after birth. Patient 4 had jejunal atresia requiring corrective surgery at 5 days of age. Patient 5 was born with congenital cutaneous candidiasis, and she is the only known survivor of this entity with a birth weight <1,500 g.16 She had numerous negative systemic cultures (blood, CSF, and urine) documented prior to the onset of her septicemia at 1 month of age. Two infants (patients 4 and 5) developed right-sided intracardiac fungal masses, an unusual complication of systemic candidiasis, which we have previously reported in another infant. Both patients were treated by surgical removal of the masses, as well as systemic antifungal therapy.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Birth Weight (g)</th>
<th>Gestational Age (wk)</th>
<th>Neonatal Problems</th>
<th>Antibiotics</th>
<th>Umbilical Lines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug</td>
<td>Arterial (d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Venous (d)</td>
</tr>
<tr>
<td>1</td>
<td>680</td>
<td>26</td>
<td>Pulmonary insufficiency of prematurity, apneic and bradycardic episodes, retrolental fibroplasia (mild)</td>
<td>A 1-7</td>
<td>1-7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G 1-7</td>
<td>1-7</td>
</tr>
<tr>
<td>2</td>
<td>1,137</td>
<td>28</td>
<td>Hyaline membrane disease, esophageal perforation, periventricular hemorrhage, retrolental fibroplasia (mild)</td>
<td>A 1-15</td>
<td>1-15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G 1-15</td>
<td>1-15</td>
</tr>
<tr>
<td>3</td>
<td>730</td>
<td>29</td>
<td>Transient tachypnea, apneic and bradycardic spells, periventricular hemorrhage</td>
<td>A 1-3</td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>G 1-3</td>
<td>...</td>
</tr>
<tr>
<td>4</td>
<td>920</td>
<td>30</td>
<td>Transient tachypnea, jejunal atresia, intraventricular hemorrhage, posthemorrhagic hydrocephalus, developmental delay</td>
<td>A 2-5, 20-30, 92-95</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>G 2-5, 20-30, 92-95</td>
<td>...</td>
</tr>
<tr>
<td>5</td>
<td>880</td>
<td>26</td>
<td>Congenital cutaneous candidiasis, hyaline membrane disease, enterococcal sepsis, periventricular hemorrhage, retrolental fibroplasia (moderate)</td>
<td>A 1-14, 27-33</td>
<td>1-17</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>G 1-14, 27-33</td>
<td>1-30</td>
</tr>
</tbody>
</table>

* Abbreviations used are: A, ampicillin sodium; G, gentamicin sulfate.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Cultures Positive for Candida albicans (Day of Life)</th>
<th>Minimal Inhibitory Concentrations (μg/mL)</th>
<th>Oral Nystatin (d)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Skin</td>
<td>Blood</td>
<td>Catheter</td>
<td>CSF</td>
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<tr>
<td>1</td>
<td>...</td>
<td>5, 7</td>
<td>6, 7</td>
<td>...</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>13-18</td>
<td>...</td>
<td>15, 16</td>
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<tr>
<td>3</td>
<td>...</td>
<td>12</td>
<td>12</td>
<td>13*</td>
</tr>
<tr>
<td>4†</td>
<td>...</td>
<td>20, 92</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5‡</td>
<td>1</td>
<td>30-33</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

* Culture negative, but increased CSF protein, decreased glucose, elevated WBC count.
† Fungal mass removed from right side of heart on day 140 was positive for C albicans.
‡ Right atrial fungal mass documented by ultrasound on day 33; removed on day 58.
A tabulation of positive cultures, drug sensitivities, and antifungal drug treatment protocols is given in Table 2. In patients 1, 2, 3, and 5, amphotericin B (0.1 mg/kg/d, intravenously [IV]) and 5-flucytosine (50 to 150 mg/kg/d, orally) were begun within 24 hours of the first positive blood culture. In patient 4, blood cultures grew C albicans on day 20 and day 92 of life. Because these cultures were felt to be contaminants, treatment was withheld. On day 136, the recognition of congestive heart failure prompted echocardiographic examination, which revealed a fungal mass in the right ventricular outflow tract. On the basis of previous cultures, antifungal therapy was begun, and patient 4 was transferred to our hospital. In all five patients, amphotericin B therapy was continued to a total dose of 13 to 38 mg/kg, during a period ranging from 17 to 95 days. All infants continued to be treated with 5-flucytosine during amphotericin B therapy. Decreased urine output, azotemia, leukopenia, thrombocytopenia, and elevated levels of liver enzyme were not observed. Hypokalemia and acidemia were observed in patient 3, but resolved with a 24-hour decrease of the amphotericin B dose.

Serum 5-flucytosine assays were performed during treatment of patients 2 (n = 1) and 5 (n = 9). When doses were normalized to 25 mg/kg per dose for comparison, mean levels at a steady state were 57 ± 10 µg/ml. No statistically significant difference existed among levels drawn at 1 (n = 3), 2 (n = 4), and 3 (n = 3) hours. No tₚ data could be extracted. Drug clearance based on average steady-state levels was calculated to be 1.2 mL/kg/min. In patient 3, one CSF level of 43 µg/mL was obtained three hours following a 25-mg/kg oral dose. No serum drug concentration monitoring for amphotericin B was performed.

All five patients recovered and have been followed sequentially for periods ranging from 4 months to 2 years. They appear to have no sequelae directly related to their infection, with the exception of patient 5, who has severe scarring of the anterior chamber of her left eye.

DISCUSSION

Over the past 20 years, 26 cases of postnatally acquired systemic candidiasis have been reported in infants with birth weight <1,500 g. Only 12 of these infants (46%) have survived; at least three (25%) of these survivors had either severe mental retardation or hydrocephalus. When an additional 14 infants in this birth-weight category with congenital candidiasis are included, all of whom died, the mortality for systemic candidiasis in very low-birth-weight infants is 70%.

Numerous factors either predispose to, or are associated with, systemic candidiasis. Neither an infant’s microbial defenses nor normal anatomic barriers (eg, skin, gastrointestinal mucosa) may be adequate to localize and protect an extremely premature infant from fungal invasion. Compromise of the gastrointestinal mucosa, from asphyxia, necrotizing enterocolitis, or surgical procedures may allow the systemic invasion of the organism. In addition, several common practices in newborn intensive care units, such as insertion of indwelling catheters, provision of parenteral nutrition, and administration of broad-spectrum antibiotics, are associated with an increased risk of systemic disease. When all factors are taken into account, it is understandable that systemic candidiasis can be a common infection in premature infants, occurring with an incidence of 3% in our study and 4% in the study of Baley et al, among infants with birth weight <1,500 g.

The diagnosis of systemic candidiasis in very small infants can be difficult. In a retrospective review of the 26 reported patients, five infants (19%) had evidence of disseminated or focal disease at autopsy, but negative systemic cultures (urine, blood, and CSF) prior to death. A review of 79 cases revealed a similar statistic (21%) in patients >1 year of age. In situations such as these, alternative means of diagnosis, such as gas-liquid chromatography of the patient’s serum for fungal components, may be a useful technique. However, systemic disease can exist without this test being positive. Serodiagnosis is not practical in most situations due to an immature immune response and the usual rapid progression of untreated disease in extremely premature infants. Frequent microscopic examination and/or culture of the urine, as well as regular fundoscopic examination in suspect infants, may permit earlier diagnosis because of the predilection for Candida involvement of these sites.

The discrimination between systemic candidiasis and transient candidemia is important in older patients, as removal of indwelling catheters and/or discontinuing broad-spectrum antibiotics or steroids has resulted in the resolution of transient infection in adults. This almost assuredly does not happen in premature infants, who cannot localize and combat such infections. To our knowledge, there is only one report of candidemia resolving in a small premature infant without treatment.

Analysis of 31 cases of systemic candidiasis in infants weighing <1,500 g (including patients 1 to 5) revealed that CSF (52%), urine (48%), and blood (45%) are the sites from which positive cultures were most commonly obtained. Other sites of
involvement documented by culture or postmortem morphology include bones/joints (26%), eye (23%), lung (13%), skin abscesses (10%), heart (6%), and peritoneum (3%). The high percentage of patients with meningitis and osteoarthritis in infancy has been noted previously, and is in contrast to findings in older children and adults who have a 2.5% and 3.7% incidence of involvement at these sites, respectively.22

Review of 19 previous case reports on systemic candidiasis, as well as the five infants in this study, indicate that, aside from the presence of Candida in the blood, the organisms are commonly found in more than one deep-seated focus. Sufficient data have been obtained from these cases and our own five patients (a total of 28 cases) to analyze the foci of infection. In these, 21/28 (75%) turned out to be multifocal with Candida involvement of more than one organ system, as listed above. The seven cases of unifocal infection include three cases of osteoarthritis,5,10 two with meningitis (patients 1, and 3), two with brain abscess,11 one with renal abscess,13 and one case of isolated pulmonary involvement.1

The most effective treatment for disseminated candidiasis has been amphotericin B and 5-flucytosine. The majority of successfully treated patients (10/12)2,3,6-10,15 and all five of our infants were treated with a combination of these drugs. One patient with isolated renal involvement was cured with nephrectomy alone.13 One infant was treated systemically with miconazole,17 and one infant was treated with amphotericin B alone.12 The combination of amphotericin B and 5-flucytosine appears to be extremely effective. However, both have been associated with serious side effects.22 The toxicity of the drugs, particularly the renal side effects of amphotericin B, may be one reason why definitive therapy has often been delayed for premature infants with positive systemic cultures.

Although the side effects of amphotericin B are a significant problem in older children and adults,26 the drug has been well tolerated by premature infants. None of 16 reported infants2-16 or our five infants with birth weight <1,500 g who received amphotericin B suffered any significant toxic effects. 5-Flucytosine has been reported to cause several side effects, including blood dyscrasia and hepatic damage.26 These side effects, however, have never been reported in premature infants receiving dosages ranging from 50 to 200 mg/kg/d.

The clinical data and treatment of 12 infants for whom sufficient details were present to analyze antifungal therapy are shown in Table 3. The majority of these infants were started at low doses (0.1 to 0.25 mg/kg/d) of amphotericin B and gradually advanced to a maximum dose of 0.5 to 1.0 mg/kg/d. Although severe side effects have not as yet been reported with a maximal daily dose of 1 mg/kg, a dose of 0.25 to 0.5 mg/kg/d appears to be equally as effective6 (patients 1, 2, 3, and 5) and may be better tolerated by extremely ill patients.

Neither the total dosage of amphotericin B nor the length of time required for successful treatment of systemic candidiasis in very premature infants

### TABLE 3. Course of Therapy for Systemic Candidiasis in 12 Infants with Birth Weight <1,500 Grams

<table>
<thead>
<tr>
<th>Reference</th>
<th>Foci of Infection</th>
<th>Treatment</th>
<th>Amphotericin B</th>
<th>5-Flucytosine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Blood CSF Urine Eye Joint</td>
<td>Other</td>
<td>Total Dose (mg/kg)</td>
<td>Maximum Daily Dose (mg/kg)</td>
</tr>
<tr>
<td>Baley et al15</td>
<td>× × × ×</td>
<td>Abscess</td>
<td>15 mg</td>
<td>?</td>
</tr>
<tr>
<td>Palmer12</td>
<td>× × × ×</td>
<td></td>
<td>10 mg</td>
<td>1.0</td>
</tr>
<tr>
<td>Svirsky-Fein et al10</td>
<td>× × × ×</td>
<td></td>
<td>40 mg</td>
<td>1.0</td>
</tr>
<tr>
<td>Rao and Myers9</td>
<td>× × × ×</td>
<td></td>
<td>25 mg*</td>
<td>1.0</td>
</tr>
<tr>
<td>Chesney et al7</td>
<td>× × × ×</td>
<td></td>
<td>19 mg</td>
<td>1.0</td>
</tr>
<tr>
<td>Keller et al6</td>
<td>× × × ×</td>
<td></td>
<td>3.7 mg*</td>
<td>0.25</td>
</tr>
<tr>
<td>DiLiberti and Hughes3</td>
<td>× × × ×</td>
<td></td>
<td>28 mg</td>
<td>0.25</td>
</tr>
<tr>
<td>This study, patient No.</td>
<td>× × × ×</td>
<td></td>
<td>?†</td>
<td>?</td>
</tr>
</tbody>
</table>

- Treatment failure.
- Intrathecal or intraventricular therapy.
is known. In evaluating these treatment data, two groups of infants can be identified. The first group had evidence of CNS, renal, or ocular involvement, and the second group had evidence of bone, joint, or cardiac involvement. Although the second group was treated with a higher total dose (33 ± 6 mg/kg v 14 ± 3 mg/kg) for a longer period of time (51 ± 27 days v 21 ± 8 days), these data cannot be easily translated into recommendations for treatment, because a lower dose of the drug for a shorter period of time might have been adequate treatment for these infections.

The intrathecal,5,9 intraventricular,2 intraarticular,5 and intraocular27 injection of amphotericin B has been reported as adjunctive treatment to systemic administration of the drug.26 However, infections of the CNS7-15 (patients 1 and 3), skeleton,3,6,9,10 and the eye12,16 (patient 5) can resolve without the use of local amphotericin B injection. This is particularly important in the CNS, as paraparesis and blindness have been reported as complications of intrathecal amphotericin B injection.25

Despite the fact that 5-flucytosine has been used as the only treatment in a number of systemic fungal infections,26 it perhaps is best used in conjunction with amphotericin B in this age group. Two infants treated primarily with 5-flucytosine (Table 3) eventually required amphotericin B in order to eradicate the infections completely.3,6 Although the drug has often been continued after the discontinuation of amphotericin B5,7,10 (patient 1), secondary resistance has developed in patients receiving 5-flucytosine alone.26,27

As with amphotericin B, the optimum daily dose, total dosage, and length of time of treatment with 5-flucytosine are unknown in this group of infants. The length of treatment has ranged from 30 to 120 days, and the daily dosage has ranged from 50 to 200 mg/kg/d (Table 3). Although the pharmacokinetic data obtained from our patients are based on an extremely limited population, they point out that treatment with 100 mg/kg/d given in four equally divided doses can result in generally adequate therapeutic levels which are well below the level (80 μg/mL) associated with bone marrow and hepatic toxicity.26

The primary goal in the management of systemic candidiasis in very premature infants should be prevention. The use of oral prophylactic nystatin has been reported as a means of limiting overgrowth of yeast in the gut, thus preventing systemic invasion.23,24,28 Although antifungal prophylaxis has been effective in a variety of patients at risk for systemic candidiasis,28 four of our five patients had received oral nystatin from birth, but still developed systemic disease. As neither toxicity nor primary and secondary resistance to nystatin has been reported in infants,28 its use may be justified; however, its efficacy remains to be demonstrated.

Exposure to factors that predispose to systemic candidiasis should be minimized. The use of broad-spectrum antibiotics should be limited to specific indications. Indwelling catheters should be used only as long as necessary and cared for with fastidious sterile technique. In infants who develop Candida septicemia, indwelling catheters should be removed immediately, as they can be a source of ongoing candidemia. Use of antibiotics should probably be discontinued, unless there are specific indications for continuing therapy, as antibiotics have been shown to enhance experimental Candida infection in laboratory animals.20

The most important aspect of treatment of fungal septicemia in extremely premature infants is the early initiation of systemic antifungal therapy. The literature, as well as our patient population, demonstrates that systemic cultures positive for C albicans must never be ignored. As amphotericin B and 5-flucytosine are well tolerated when used carefully, there is no reason not to initiate therapy while a comprehensive search is begun for foci of infection. Examination of the CSF and skeletal system is necessary, because premature infants have a high incidence of meningitis and osteoarthritis. Infants who have had indwelling right atrial catheters should have an echocardiogram performed to determine whether a right-sided cardiac fungal mass is present. All of our patients did well, although all isolates of C albicans were extremely sensitive to both drugs. Initiation of aggressive early therapy, combined with elimination of predisposing factors, may not guarantee fewer complications, but the outcome for our patients was substantially better than has been previously reported.

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