Effects of Fluid and Electrolyte Management on Amphotericin B-Induced Nephrotoxicity Among Extremely Low Birth Weight Infants

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ABSTRACT. Objective. Greater use of invasive procedures and aggressive antimicrobial therapy predisposes extremely low birth weight (ELBW) infants to systemic fungal sepsis. Despite its adverse effects (including renal and electrolyte disturbances), amphotericin B (amphoB) remains the preferred drug for fungal therapy. Multiple studies have indicated that sodium loading may prevent renal toxicity among animals and human adults. The effects of fluid and electrolyte management on amphoB-induced nephrotoxicity among ELBW infants have not been evaluated extensively. The purpose of this study was to examine the effects of fluid and electrolyte management on amphoB-induced nephrotoxicity among ELBW infants.

Design/Methods. The medical records were reviewed for all ELBW infants (birth weights of ≤1250 g) who developed systemic fungal sepsis, requiring amphoB therapy, between January 1992 and December 2000. Demographic, clinical, and laboratory data were collected from the medical records for each patient.

Results. Fungal sepsis requiring amphoB treatment developed for 4.4% of ELBW infants (25 of 573 infants), with a gestational age of 25 ± 1 weeks and a birth weight of 738 ± 37 g, at a postnatal age of 16 ± 2 days. Renal compromise, as manifested by low urine output and high creatinine levels, occurred for 44% of those infants (11 of 25 infants). There was no difference between the infants who developed renal compromise (renal compromise group [RCG], n = 11) and those who did not (no-renal-compromise group [NCG], n = 14) with respect to birth weight, gestational age, and risk factors predisposing the infants to fungal sepsis. The RCG demonstrated a decrease in urine output by 3.4 ± 2 days and an increase in serum creatinine levels by 3.9 ± 2 days after the initiation of amphoB therapy. Infants in the RCG had a significantly higher incidence of hyponatremia, compared with infants in the NCG (7 of 11 infants vs 0 of 14 infants), with no significant difference in the incidences of hyperkalemia (2 of 11 infants vs 0 of 14 infants). Infants in the RCG, compared with infants in the NCG, had significantly lower mean daily sodium intakes in the 4 days before the initiation of amphoB therapy (2.6–2.9 mEq/kg per day vs 4.2–4.7 mEq/kg per day) and in the first 4 days of amphoB treatment (2.7–3.1 mEq/kg per day vs 4.5–5.6 mEq/kg per day). Mean daily sodium intakes were not statistically significantly different between the 2 groups between day 5 and day 10 of amphoB therapy. Infants in the RCG tended to have lower mean daily potassium intakes in the 4 days before the initiation of amphoB therapy and during the first 4 days of amphoB therapy. Subsequently, the mean daily potassium intakes remained not statistically significantly different between the groups. Mean daily fluid intakes were not different between the groups.

Conclusions. Conventional amphoB combined with adequate hydration and higher sodium intakes of >4 mEq/kg per day may provide effective protection against amphoB-induced nephrotoxicity among ELBW infants. Our data confirm the published results of animal and human adult studies and suggest that higher sodium intakes may prevent renal compromise during amphoB therapy among ELBW infants. Pediatrics 2004; 113:e608–616. URL: http://www.pediatrics.org/cgi/content/full/113/6/e608; amphotericin B, nephrotoxicity, ELBW infants.

ABBREVIATIONS. RCG, renal compromise group; NCG, no-renal-compromise group; ELBW, extremely low birth weight; amphoB, amphotericin B.

The advances in neonatal intensive care have led to increases in the survival rates for extremely low birth weight (ELBW) infants.1 The invasive treatment modalities required by ELBW infants increase their risk for nosocomial infections, which are associated with significant rates of death and morbidity, including ophthalmologic, visceral, and cardiac abnormalities and meningitis.2–4 Candida species have been identified as the third most common organisms for late-onset sepsis among very low birth weight infants.4 Moreover, Kossoff et al5 reported that the rate of candidemia in their neonatal intensive care unit increased 11-fold between 1981 and 1995. Because systemic fungal infections are associated with mortality rates of 15% to 60% in reported cases, early initiation of therapy is warranted.6–10 Rapid diagnosis and treatment of such infections are hindered by the high incidence of fungus that is undetectable in cultures and the long periods needed for fungal growth.11

With a questionnaire sent to United States-based pediatric infectious disease specialists and neonatologists, Rowen et al12 found that 88% of respondents considered amphotericin B (amphoB) the therapy of choice for fungal sepsis. AmphoB has been favored because of its fungicidal effects.12 Unfortunately, am-
Amphotericin B therapy is associated with adverse effects, including infusion reactions with hemodynamic and temperature instability, thrombocytopenia, and nephrotoxicity with electrolyte disturbances. Concern regarding these adverse reactions has contributed to hesitation in beginning empiric treatment before positive culture findings are obtained. Efforts to reduce these side effects have led to the development of amphotericin-lipid formulations and research on the effects of salt supplementation before amphotericin B therapy. Conventional amphotericin B is preferred over the liposomal preparations because it achieves higher concentrations in renal tissue, which is an important consideration because 20% to 40% of infants demonstrate renal involvement.

Multiple studies have indicated that adequate fluid and electrolyte balances before amphotericin B administration may prevent renal toxicity. Studies of animals and human adults have demonstrated that salt loading before amphotericin B therapy ameliorates the nephrotoxicity. The effects of fluid and electrolyte management on amphotericin B-induced nephrotoxicity among ELBW infants have not been extensively evaluated. The purpose of this study was to assess the effects of fluid and electrolyte (including sodium and potassium) management on amphotericin B-induced renal compromise among ELBW infants with birth weights of ≤1250 g.

**DESIGN/METHODS**

Medical records were reviewed for all ELBW infants with birth weights of ≤1250 g who developed systemic fungal infections that required amphotericin B therapy between January 1992 and December 2000. The infants were admitted to the neonatal intensive care unit at Sparrow Hospital (Lansing, MI). The institutional review board of the hospital approved the study.

Demographic, clinical, and laboratory information was collected from the medical records of each patient. Demographic data included gestational age, birth weight, gender, race, and Apgar scores. The charts were reviewed for clinical data such as symptoms and signs of infection and laboratory data including culture results. Infants with fungal sepsis presented with at least 2 of the following clinical manifestations: increased ventilatory support, increased apnea and bradycardia, hyperglycemia, hypotension, acidosis, leukopenia, leukocytosis, or thrombocytopenia.

For all infants with fungal sepsis, blood, urine, cerebrospinal fluid, and endotracheal aspirate cultures were obtained. If the cultures for any of those sites yielded positive results, then repeat cultures were performed every 1 to 2 days until the cultures yielded negative results. In addition, all infants with fungal sepsis underwent fundal examinations performed by a pediatric ophthalmologist, as well as renal ultrasonographic and echocardiographic evaluations. Infants were treated with antifungal drugs for a minimum of 7 days after the first persistent negative culture. The following data were collected to assess the risk factors for developing systemic fungal infections: number of ventilator days, number of central line days, postnatal corticosteroid use, number of transfusions, amount of intralipid administered, and use of antibiotics before the diagnosis of fungal infection.

The following data regarding fungal sepsis were recorded: age of infant at time of diagnosis, *Candida* species, infection site, number of positive cultures, and time to achieve negative cultures. During the study period, our protocol was to initiate amphotericin B therapy with a test dose of 0.1 mg/kg. If the patient tolerated the test dose, then the amphotericin B dose was gradually increased by 0.1 mg/kg per day to a maximal dose of 0.5 to 1 mg/kg per day for the duration of treatment. The length of amphotericin B therapy, the time to reach 0.5 mg/kg per day, the dose of amphotericin B used until renal compromised occurred, and the total dose were recorded. We also examined the use of nephrotoxic drugs (gentamicin, tobramycin, vancomycin, and indomethacin) before and during amphotericin B therapy.

The effects of fluid and electrolyte management on amphotericin B-induced nephrotoxicity were examined by collecting data on serum creatinine, sodium, and potassium concentrations. Daily fluid intake and urine output, as well as sodium and potassium supplementation, were also recorded. Fluid and electrolyte data were collected for 4 days before the initiation of amphotericin B therapy. These data were used as the baseline values for the study infants. Serum electrolyte and creatinine concentrations for evaluation of potential nephrotoxicity were obtained at the initiation of therapy, every other day for the first 2 weeks, and twice weekly thereafter. Fluid and electrolyte management was at the discretion of the attending physician.

The patients were then divided into 2 groups, depending on the presence of renal compromise, ie, the renal compromise group (RCG) and the no–renal-compromise group (NCG). Renal compromise was defined as an increase in serum creatinine levels of >1 mg/dL or >50%, oliguria of <1 mL/kg per hour, or a decrease in urine output of 50%. Hyponatremia was diagnosed when the serum sodium concentration was <130 mEq/dL; hypokalemia was diagnosed when the serum potassium concentration was <3 mEq/dL.

Fluid and electrolyte data were analyzed for 3 time periods, ie, 4 days before amphotericin B therapy, 4 days after the initiation of amphotericin B therapy, and days 5 to 10 after the initiation of amphotericin B therapy. These periods were selected on the basis of the development of renal compromise in the RCG by a mean of 4 days and its resolution by a mean of 9 days after the initiation of amphotericin B therapy.

The demographic and clinical data for the 2 groups were examined and reported as mean ± SD. The continuous data with normal distribution were compared by using Student's *t* test. The Mann-Whitney rank sum test was used if the normality test failed. The ordinal data were compared by using Fisher's exact test. Significance was accepted at *P* < .05.
RESULTS

A total of 573 infants with birth weights of ≤1250 g were admitted during the study period. *Candida* species were isolated from blood, urine, or tracheal aspirates for 26 patients. All cerebrospinal fluid cultures yielded negative results. One patient was treated with liposomal amphoB and was excluded. The remaining 25 infants were treated with conventional amphoB and were included in the study. None of those infants exhibited congenital anomalies.

Two infants in the RCG expired. One expired on day 7 of amphoB treatment, as a result of overwhelming sepsis and acute renal failure. The death of the second infant occurred after amphoB therapy had been completed and was unrelated to fungal infection. The data for both infants were included.

The demographic data for both groups are presented in Table 1. The characteristics of all infants in the study were appropriate for gestational age. There was no significant difference in gestational age, birth weight, gender, or postnatal age at the time of fungal sepsis diagnosis.

There was no significant difference in the clinical presentation of the study infants at the time of fungal sepsis diagnosis, as summarized in Table 1. None of the patients exhibited necrotizing enterocolitis near the time of diagnosis of fungal sepsis, and the incidences of thrush and diaper rash were not significantly different between the 2 groups. There was no statistically significant difference between the 2 groups with respect to the risk factors for developing systemic fungal sepsis, including the number of ventilator days, the number of central line days, postnatal corticosteroid use, the number of transfusions, and the amount of intralipid administered before amphoB therapy, as summarized in Table 2. There was no difference in the concomitant use of amphoB and antibiotics between the 2 groups. The interval from the last administration of antibiotics to the diagnosis of fungal sepsis tended to be shorter in the RCG. None of the study infants received indomethacin within 7 days before amphoB therapy. *Candida albicans* was the most common organism in both groups (10 of 11 cases vs 7 of 14 cases, *P* = .08). Other fungal species included *Candida parapsilosis*, *Candida tropicalis*, *Candida lumbica*, *Malassezia*, and 1 unidentified *Candida* species. Table 3 summarizes the fungal infection sites. There was no significant difference between the 2 groups in the numbers of infants for whom fungus was isolated from multiple sites (8 of 11 infants vs 4 of 14 infants, *P* = not significant). There was also no difference between the 2 groups in the numbers of renal fungal infections (6 of 11 infants vs 7 of 14 infants, *P* = not significant). For 1 patient in each group, fungal balls were identified with renal ultrasonography. One patient in the RCG exhibited both renal and ocular evidence of fungus. None of the patients demonstrated cardiac vegetation. There was no significant difference between the groups in the mean postnatal age at the time of fungal sepsis diagnosis (15 vs 16 days, *P* = not significant), the mean length of therapy (15 vs 18 days, *P* = not significant), the mean cumulative amphoB dose at the time of renal compromise (2 vs 2.8 mg/kg, *P* = not significant), or the mean total dose of amphoB (14.5 vs 17 mg/kg, *P* = not significant).

The dose and frequency of amphoB treatment were not changed for any of the infants with amphoB-induced nephrotoxicity. There was no difference in the incidences of renal dysfunction with elevated serum creatinine levels of >1 mg/dL before the initiation of amphoB treatment between the groups (4 of 11 infants vs 3 of 14 infants, *P* = not significant). The serum creatinine concentrations normalized for 2 of the 4 RCG patients before the initiation of amphoB treatment. However, after the initiation of amphoB treatment, serum creatinine levels increased by >50% for all 4 patients. The renal dysfunction in the 3 NCG infants resolved before the initiation of amphoB therapy. Mean daily serum creatinine levels tended to be higher in the RCG than in the NCG, and the difference achieved statistical significance between days 4 and 6 of amphoB therapy (Fig 1). The increase in serum creatinine levels in the RCG occurred at 3.9 ± 2 days and was preceded by a decrease in urine output at 3.4 ± 2 days after the initiation of amphoB therapy. Increases in serum

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Data and Clinical Characteristics of Study Infants at the Time of Fungal Sepsis Diagnosis</th>
<th>RCG (n = 11)</th>
<th>NCG (n = 14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestation age, wk</td>
<td>25 ± 1.8</td>
<td>25.3 ± 1.7</td>
<td>.6</td>
</tr>
<tr>
<td>Median (range), wk</td>
<td>25 (23–29)</td>
<td>25 (23–29)</td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>740 ± 211</td>
<td>729 ± 150</td>
<td>.88</td>
</tr>
<tr>
<td>Median (range), g</td>
<td>665 (716–1250)</td>
<td>702 (535–1035)</td>
<td></td>
</tr>
<tr>
<td>Gender (male/female), no.</td>
<td>9/5</td>
<td>5/6</td>
<td>.4</td>
</tr>
<tr>
<td>Survival, no.</td>
<td>9/11</td>
<td>14/14</td>
<td>1.0</td>
</tr>
<tr>
<td>Increase ventilatory support, no.</td>
<td>6</td>
<td>8</td>
<td>.1</td>
</tr>
<tr>
<td>Increased apnea and bradycardia, no.</td>
<td>2</td>
<td>4</td>
<td>.7</td>
</tr>
<tr>
<td>Hypotension, no.</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Metabolic acidosis, no.</td>
<td>3</td>
<td>2</td>
<td>.6</td>
</tr>
<tr>
<td>Hyperglycemia, no.</td>
<td>4</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia, no.</td>
<td>7</td>
<td>7</td>
<td>.6</td>
</tr>
<tr>
<td>Leukocytosis, no.</td>
<td>7</td>
<td>9</td>
<td>.1</td>
</tr>
<tr>
<td>Leukopenia, no.</td>
<td>3</td>
<td>2</td>
<td>.6</td>
</tr>
<tr>
<td>Diaper rash/thrash, no.</td>
<td>9</td>
<td>10</td>
<td>.7</td>
</tr>
</tbody>
</table>

Values represent mean ± SD or number of cases. The 2 groups were compared with Student’s *t* test or the Mann-Whitney rank sum test. Ordinal data were compared with Fisher’s exact test.
TABLE 2. Treatment Data for Study Infants

<table>
<thead>
<tr>
<th>No. of Positive Fungal Cultures*</th>
<th>RCG (n = 11)</th>
<th>NCG (n = 14)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range)</td>
<td>5 ± 3</td>
<td>4 ± 3</td>
<td>.32</td>
</tr>
<tr>
<td>Median (range)</td>
<td>5 (1-12)</td>
<td>3.5 (1-10)</td>
<td>.85</td>
</tr>
<tr>
<td>Time until initiation of amphoB therapy, d†</td>
<td>4.3 ± 4.4</td>
<td>4.1 ± 3.8</td>
<td>.85</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (0-16)</td>
<td>2 (0-11)</td>
<td>.31</td>
</tr>
<tr>
<td>Time to negative fungal culture, d‡</td>
<td>10.8 ± 9</td>
<td>7.8 ± 5</td>
<td>.31</td>
</tr>
<tr>
<td>Median (range)</td>
<td>7 (2-33)</td>
<td>8 (3-16)</td>
<td>.85</td>
</tr>
<tr>
<td>Length of therapy after negative culture, d</td>
<td>11.2 ± 4.6</td>
<td>13.7 ± 6.4</td>
<td>.29</td>
</tr>
<tr>
<td>Median (range)</td>
<td>11 (7-21)</td>
<td>11 (7-25)</td>
<td>.58</td>
</tr>
<tr>
<td>Total length of therapy, d</td>
<td>17 ± 10</td>
<td>19 ± 9</td>
<td>.58</td>
</tr>
<tr>
<td>Median (range)</td>
<td>14 (7-41)</td>
<td>16 (8-30)</td>
<td>.23</td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.1 (0.6-5.5)</td>
<td>2.5 (0.2-5.5)</td>
<td></td>
</tr>
<tr>
<td>Total cumulative amphoB dose, mg/kg§</td>
<td>14.5 ± 10.1</td>
<td>17 ± 11</td>
<td>.6</td>
</tr>
<tr>
<td>Median (range), mg/kg</td>
<td>10.3 (3.6-33.5)</td>
<td>15.4 (2.75-38)</td>
<td></td>
</tr>
<tr>
<td>Ventilation days</td>
<td>15 ± 11</td>
<td>16 ± 8</td>
<td>.83</td>
</tr>
<tr>
<td>Median (range)</td>
<td>10 (1-35)</td>
<td>16.5 (0-29)</td>
<td>.81</td>
</tr>
<tr>
<td>Central line days</td>
<td>14.3 ± 12</td>
<td>13.4 ± 6.2</td>
<td>.81</td>
</tr>
<tr>
<td>Median (range)</td>
<td>9 (1-13)</td>
<td>13 (7-30)</td>
<td>.31</td>
</tr>
<tr>
<td>Lipids before diagnosis, g/kg</td>
<td>16.1 ± 17.5</td>
<td>23 ± 15.3</td>
<td>.31</td>
</tr>
<tr>
<td>Median (range), g/kg</td>
<td>6.8 (0.55-2)</td>
<td>25.4 (1.8-52)</td>
<td></td>
</tr>
<tr>
<td>No. of blood transfusions</td>
<td>10.9 ± 6.2</td>
<td>8.9 ± 6.7</td>
<td>.44</td>
</tr>
<tr>
<td>Median (range)</td>
<td>13 (0-19)</td>
<td>8.5 (1-23)</td>
<td>.35</td>
</tr>
<tr>
<td>Postnatal steroid days</td>
<td>0.9 ± 2.2</td>
<td>2.7 ± 3.9</td>
<td>.35</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0 (0-7)</td>
<td>0 (0-10)</td>
<td></td>
</tr>
<tr>
<td>Concomitant antibiotics</td>
<td>9/11</td>
<td>10/14</td>
<td>1.0</td>
</tr>
<tr>
<td>Concomitant nephrotoxic drugs</td>
<td>7/11</td>
<td>9/14</td>
<td>1.0</td>
</tr>
<tr>
<td>Days since last dose of antibiotic</td>
<td>2.7 ± 2.3</td>
<td>5.9 ± 5.6</td>
<td>.09</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3 (0-7)</td>
<td>4 (0-19)</td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean ± SD. The 2 groups were compared with Student’s t test or the Mann-Whitney rank sum test. Ordinal data were compared with Fisher’s exact test. P < .05 indicates significance.

* This represents the total number of positive cultures. Some of these could have been obtained on the same day or different days or from different sites.

† This represents the time from obtaining the culture to the initiation of amphoB therapy. Some positive cultures were thought to be contaminated and amphoB treatment was started after repeated cultures became positive.

‡ This represents the time from the drawing of the first positive culture to the first persistent negative culture.

§ This represents the cumulative amphoB dose at the time of renal compromise. Each infant in the RCG was matched by 1 infant in the NCG.

TABLE 3. Fungal Infection Sites

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>RCG (n = 11)</th>
<th>NCG (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Urine</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tracheal aspirate</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Blood/urine</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Blood/tracheal aspirate</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Urine/tracheal aspirate</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Eyes, blood, and urine</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Creatinine concentrations of >50% occurred for 8 of 11 infants, and decreases in urine output of >50% occurred for 9 of 11 infants. Renal compromise lasted for a period of 5.5 ± 4.7 days and resolved on day 8.8 ± 5.4 of amphoB therapy.

Serum sodium concentrations and daily sodium supplementation are summarized in Fig 2. In the 4 days before the initiation of amphoB treatment, none of the patients in either group demonstrated hyponatremia. RCG infants exhibited a significantly higher incidence of hyponatremia, compared with NCG infants (7 of 11 infants vs 0 of 14 infants, P < .04), during the first 10 days of treatment. Hyponatremia was not associated with excessive weight gain (Fig 3). The mean daily sodium intake in the 4 days before amphoB therapy was statistically significantly lower in the RCG than in the NCG (2.6–2.9 mEq/kg per day vs 4.2–4.7 mEq/kg per day, P < .005) (Fig 2). In addition, the mean daily sodium intake during the first 4 days of treatment was significantly lower in the RCG (2.7–3.1 mEq/kg per day vs 4.5–5.6 mEq/kg per day, P < .04). During the first 4 days of amphoB therapy, the mean daily sodium intake was <3 mEq/kg per day for 6 of 11 infants in the RCG and no infants in the NCG (P < .001). None of the infants in the RCG and 9 of 14 infants in the NCG (P < .001) demonstrated a mean daily sodium intake of >4 mEq/kg per day (Table 4). The difference in the mean daily sodium intake values between the groups was not statistically significant between day 5 and day 10 of amphoB therapy (3.8–4.6 mEq/kg per day vs 4.3–5.6 mEq/kg per day, P = not significant). Even when we examined the mean daily sodium intake before the development of renal compromise, the RCG infants exhibited a statistically significantly lower sodium intake, compared with the NCG infants (1.1–3.9 mEq/kg per day vs 3–10.3 mEq/kg per day, P = .003) (Table 5). We also evaluated the mean daily sodium intake for each individual infant in the RCG and found that those infants demonstrated sta-
Fig 1. Mean serum creatinine concentrations during the study period.

Fig 2. Serum sodium concentrations and daily mean sodium intake 4 days before and 10 days after the initiation of amphoB therapy.
tistically significantly lower mean daily sodium in-
takes before the development of renal compromise,
compared with those after renal compromise (1.1–3.9
mEq/kg per day vs 3.3–6.4 mEq/kg per day, P = .006) (Table 5).

RCG infants tended to have lower mean daily
potassium intakes in the 4 days before the initiation
of amphoB therapy (1.8–2.2 mEq/kg per day vs 2.1–
2.6 mEq/kg per day, P = not significant) and in the
first 4 days of amphoB therapy (1.6–1.9 mEq/kg per
day vs 2.2–2.6 mEq/kg per day, P = not significant)
(Fig 4). In the subsequent days of treatment, the 2
groups did not differ with respect to mean daily
potassium intakes. The incidences of hypokalemia
were not significantly different between the groups
(2 of 11 infants vs 0 of 14 infants, P = not significant).
There was no significant difference in the mean daily

Fig 3. Fluid intake, urine output, and daily weight changes for 4 days before amphoB therapy and during the study period.

DISCUSSION
ELBW infants are at high risk of developing sys-
temic fungal infections. Host factors such as imma-
turity of the immune system and prolonged use of
antibiotics make such infants more vulnerable. Systemic fungal infections among ELBW infants have become a problem of increasing magnitude. Our incidence of 4.5% is within the range reported in the literature. AmphoB remains the drug of choice for treating systemic candidiasis. Concomitant antibiotic and nephrotoxic drug use or previous antibiotic treatment did not influence the incidence of amphoB nephrotoxicity in our study. Other risk factors, such as the number of central line catheter days, the number of ventilation days, the number of transfusions, postnatal corticosteroid use, and intralipid use did not seem to influence the incidence of amphoB nephrotoxicity in this study.

AmphoB belongs to the class of polyene antibiotics, which are characterized by lipophilic and hydrophilic regions. Free amphoB acts by binding to sterols in cell membranes, especially ergosterol in fungal membrane and to a lesser degree cholesterol in mammalian cells. Because renal tubular cells are high in cholesterol, nephrotoxicity is an undesirable side effect of amphoB therapy.

Two strategies have been demonstrated to ameliorate renal toxicity, i.e., incorporation into a liposomal amphotericin system and salt loading before amphoB administration. Although some clinical trials have demonstrated decreased nephrotoxicity with the use of liposomal amphoB, other controlled clinical trials have failed to demonstrate improved outcomes or decreased mortality rates, compared with conventional amphoB. Furthermore, liposomal preparations are more costly.

Salt loading before amphoB administration can reduce nephrotoxicity effectively, as demonstrated in animal and human adult studies, and is inexpensive. The exact mechanism by which sodium reduces the incidence and severity of amphoB-induced nephrotoxicity has not been clearly delineated. The 2 nonexclusive postulated mechanisms of nephrotoxicity suggested in the literature include changes in membrane permeability and drug-induced preglomerular vasoconstriction. Animal studies have suggested that enhancement of tubuloglomerular feedback is a mechanism for amphoB-induced nephrotoxicity. It was demonstrated that tubuloglomerular feedback could be blocked by salt loading. Sawaya et al demonstrated that systemic and afferent arteriolar vasoconstriction was a second mechanism of amphoB-induced nephrotoxicity in a single-nephron model.

Reports on human adults have included mainly case reports and retrospective studies. Llanos et al reported the only prospective, double-blind, placebo-controlled trial. They treated 20 adult male patients with amphoB (50 mg per dose) 3 times per week for 10 weeks. In that study, 10 patients received 1 L of 0.9% saline solution, whereas the other 10 patients received 1 L of 5% dextrose solution. The serum creatinine levels increased and the creatinine clearance values decreased in the dextrose-treated group; the parameters were not affected in the saline-treated group.

Most of the published studies investigated the effect of sodium loading in decreasing amphoB-induced nephrotoxicity, whereas our study examined the effect of total sodium intake in ameliorating amphoB-induced nephrotoxicity. Studies of human adults have used 85 to 600 mEq/day of sodium before amphoB administration. The exact amount of sodium required to prevent nephrotoxicity among neonates is not known. The results of our study indicated that normal sodium intakes of 3 to 4 mEq/kg per day had some beneficial effects in preventing renal compromise, whereas sodium intakes of >4 mEq/kg per day prevented renal compromise. In the 4 days before and 4 days after the initiation of amphoB treatment, none of the infants in the RCG received >4 mEq/kg per day, compared with 8 infants in the NCG. There is no clear explanation for
the discrepancy of the sodium intakes between the 2 groups, because electrolyte management was at the discretion of the attending neonatologist. Interestingly, the increase in sodium intake in the RCG was associated with amelioration of renal compromise within 3 to 16 days of higher sodium intake. Heideman et al.\textsuperscript{38} described this phenomenon for 5 adults who developed amphotericin-induced nephrotoxicity early in the course of treatment. All patients were sodium-depleted because of underlying illnesses. Within 4 to 12 days after liberalization of dietary sodium intake (150–300 mEq/day) and discontinuation of diuretic therapy, renal function improved for all patients.\textsuperscript{38}

Other electrolytes, such as potassium, have been implicated in nephrotoxicity.\textsuperscript{22,39} A potassium-deficient diet was shown to enhance nephrotoxicity after gentamicin administration in an animal model.\textsuperscript{39} Potassium loading decreased functional and histologic evidence of gentamicin-induced nephrotoxicity.\textsuperscript{39} Bernado et al.\textsuperscript{22} reported that potassium depletion potentiated amphotericin-induced toxicity in a rat model. The study showed that potassium depletion did enhance urinary sodium excretion and potentiated the development of renal tubular toxicity. Our data showed that potassium intake tended to be lower in the RCG before the initiation of amphotericin treatment and was not significantly lower in the first 4 days of amphotericin therapy. In addition, in an evaluation of RCG infants, there was no difference in the mean daily potassium intakes before and after renal compromise. Among adults, salt loading resulted in increased urinary potassium loss. In our study, higher sodium intakes were not associated with decreases in serum potassium levels (Figs 2 and 4). It is unclear whether the modest increase in sodium intake was insufficient to trigger a change in serum potassium levels or whether the finding was attributable to differences in tubular function among ELBW infants. However, the effects of higher sodium intake on potassium homeostasis were difficult to evaluate, because urine electrolyte levels were not measured for these infants.

Clinical data for adults and animals have indicated that adequate hydration is important for the prevention of amphotericin-induced nephrotoxicity.\textsuperscript{23} We found that fluid intakes before the initiation of amphotericin therapy tended to be lower in the RCG but intakes became comparable during the first 4 days of amphotericin therapy. Furthermore, urine outputs and mean daily weight gains were comparable in the 2 groups. Therefore, it is unlikely that fluid depletion played a
role in predisposing these ELBW infants to renal compromise.

CONCLUSIONS

Our data confirm the findings of animal and human adult studies, indicating that higher sodium intakes among ELBW infants were associated with reductions in amphotericin B-induced nephrotoxicity. In times of limited resources, cost-effective treatment options are pivotal in improving the outcomes of ELBW infants. We propose that conventional amphotericin B combined with adequate hydration and sodium intakes of >4 mEq/kg per day may provide effective protection against amphotericin B-induced nephrotoxicity among ELBW infants. A prospective study to evaluate the effect of sodium loading on the prevention of amphotericin B-induced nephrotoxicity among ELBW infants with proven fungal sepsis is warranted.

REFERENCES

Effects of Fluid and Electrolyte Management on Amphotericin B-Induced Nephrotoxicity Among Extremely Low Birth Weight Infants
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