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A Comparison of AmBisome® to Amphotericin B for Treatment of Systemic Candidiasis in Very Low Birth Weight Infants

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Purpose: Amphotericin B is considered the treatment of choice for systemic candidiasis, but adverse effects may limit its use. An alternative option for the treatment of candidiasis includes lipid preparations of amphotericin B. This study investigated the safety and efficacy of AmBisome®, a lipid formulation of amphotericin B containing liposomal structures, for the treatment of systemic candidiasis in very low birth weight infants (VLBWI). **Materials and Methods:** Data from 26 VLBWI treated with AmBisome® in the study group (AmBisome group) from October 2003 to July 2006 were compared with data from 20 VLBWI treated with amphotericin B as a historical control (Amphotericin group). This study was a prospective, historical control, multi-center trial. **Results:** *Candida* spp. was isolated in 73% (19/26) of the cases for the AmBisome group and 90% (18/20) of the cases for the Amphotericin group. The fungal eradication rate and the time to eradication was 84% (16/19) and 9 ± 8 days in the AmBisome group, and 89% (16/18) and 10 ± 9 days in the Amphotericin group, respectively ($p = 0.680$ vs $p = 0.712$). The major adverse effects were lower in the AmBisome group (renal toxicity, 21% vs 55%, $p = 0.029$; hepatotoxity, 25% vs 65%, $p = 0.014$, AmBisome group vs Amphotericin group, respectively). There was no significant difference in mortality attributed to systemic candidiasis (12% in the AmBisome group, 10% in the Amphotericin group, $p = 0.868$). **Conclusion:** AmBisome® is effective and safe for treating systemic fungal infections in VLBWI.

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INTRODUCTION

The incidence of fungal sepsis in the neonatal intensive care unit (NICU) has increased recently,[1,2] and fungal sepsis is the third most common cause of late onset sepsis in the NICU.[3] Systemic candidiasis is the most common and fatal cause of fungal sepsis in newborns.[4,5] Moreover, 2-4% of neonates with systemic candidiasis are very low birth weight infants (VLBWI), weighing less than 1500 g, and have a high mortality rate.[6,7] Major risk factors for systemic candidiasis include intravenous catheter use, prolonged antibiotic therapy (particularly third-generation cephalosporin usage), mechanical ventilation, prolonged total parenteral nutrition, and prolonged hospitalization. Despite improvements in neonatal intensive care, the mortality rate in VLBWI with systemic candidiasis receiving antifungal agents is high.[1] Currently amphotericin B is considered to be the treatment of choice for systemic candidiasis but its use is limited due to adverse effects such as renal toxicity, hepatotoxicity, electrolyte imbalances, and bone marrow suppression.[8,9] Preterm infants born before 34 weeks of gestation have a significantly lower glomerular filtration rate (GFR) and renal tubular

function than full-term infants, which persists for up to 3-5 weeks post-natally.[10] In addition, many risk factors including the maternal use of non-steroidal anti-inflammatory drugs during pregnancy, respiratory distress syndrome (RDS), a low Apgar score and ibuprofen treatment are associated with impaired renal function in preterm infants.[11] The renal function of these preterm infants treated with amphotericin B is even further deteriorated as a result of renal tubular dysfunction and decreased GFR due to amphotericin B induced vasoconstriction. This deterioration in renal function may limit amphotericin B use at the proper and maximum dosage, which can cause treatment failure and a high mortality rate.

New lipid formulated amphotericin B preparations have been reported to have reduced renal toxicity compared to conventional amphotericin B while maintaining the same effectiveness, and may be a more useful alternative in patients with impaired renal function. AmBisome® is one of the lipid formulations of amphotericin B that has received considerable attention for its use in adult patients. This drug has received Food and Drug Administration (FDA) approval for the treatment of patients with 1) cryptococcal meningitis-HIV infection; 2) mycosis as an empiric therapy for a presumed fungal infection in patients with febrile neutropenia; 3) systemic mycosis due to aspergillus, candida, and cryptococcus in patients refractory to amphotericin B deoxycholate or where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate; and 4) visceral leishmaniasis.[1,12] Thus far, however, there is limited experience with the use of AmBisome® in preterm infants with systemic candidiasis, and the few reports have been limited to uncontrolled, retrospective analyses and case reports. Therefore, amphotericin B continues to be the treatment of choice in preterm infants with systemic candidiasis. This study compared the safety and efficacy of AmBisome® in the treatment of VLBWI with systemic candidiasis to that of conventional amphotericin B.

MATERIALS AND METHODS

This study was a prospective historical control multi-center study and was reviewed, approved, and funded by the institutional review board of the IN-SUNG Foundation of Medical Research (C-A4-824-1). AmBisome® is not covered by current medical insurance, and only patients with informed parental consent were enrolled in this study. Twenty-six VLBWI were treated with AmBisome® (AmBisome group) for systemic candidiasis in the NICU from October 2003 to July 2006 at various medical centers. These medical centers included the Samsung Medical Center, Sungkyunkwan University School of Medicine (n = 18), Bucheon Hospital, Soonchunhyang University, College of Medicine (n = 3), Ilsan Paik Hospital, Inje University School of Medicine (n = 2), Ansan Hospital, Korea University School of Medicine (n = 2), and the Kangnam Cha Hospital, Pochon Cha University, College of Medicine (n = 1). VLBWI treated with amphotericin B, and who were from the same hospitals, were assigned as the historical control (n = 20, Amphotericin group) and were compared with the AmBisome group. Table 1 shows details regarding enrolled hospitals.

Systemic candidiasis was defined only when the blood culture was positive for *Candida* spp. with the clinical signs of a systemic infection. A

Table 1. Details of Enrolled Hospitals

Hospital	A	B	C	D	E
AmBisome® group (n = 26)	18	3	2	2	1
Amphotericin group (n = 20)	15	1	1	1	2

A, Samsung Medical Center, Sungkyunkwan University School of Medicine; B, Bucheon Hospital, Soonchunhyang University, College of Medicine; C, Ilsan Paik Hospital, Inje University School of Medicine; D, Ansan Hospital, Korea University School of Medicine; E, Kangnam Cha Hospital, Pochon Cha University, College of Medicine.

blood culture positive for *Candida* spp. was mandatory but other cultures positive for *Candida* spp. such as urine, cerebrospinal fluid and tracheal aspirate were not required. Patients with clinical candidiasis enrolled in this study were defined as those having negative blood cultures with a suspicion of sepsis due to clinical and/or laboratory findings who did not respond to antibiotics for more than seven days. Blood (1/2 mL) was extracted from patients using a sterile technique. The blood was then inoculated into aerobic and anaerobic blood culture media (BacT/ALERT®, BioMerieux, Durham, NC, USA) and processed according to standard microbiologic techniques. Results of the blood cultures were initially reported one week after inoculation, and a final report was issued three weeks following inoculation.

Liposomal amphotericin B (AmBisome®, Gilead Sciences International Ltd., Cambridge, UK) was administered with a beginning dosage of 1 - 3 mg/kg/day which incrementally increased daily by 1 - 3 mg/kg/day until maximum dosage at 5 mg/kg/day. By this means, the target dosage was reached by the fifth day of administration with a final concentration of 1 mg/mL diluted in 5% dextrose water over a continuous two hours infusion. Amphotericin B (Fungizone®, Bristol-Myers Squibb, France) was administered with a daily dosage from 0.5 - 1.0 mg/kg/day with a final concentration of 1 mg/mL with 5% dextrose water over a continuous six hours infusion. The treatment was finished if the patients were considered to be clinically cured and received therapy until a negative blood culture from positive blood culture was observed, or if the patients with clinical candidiasis showed improved clinical and/or laboratory findings which means they responded to the antifungal therapy.

The efficacy of the two drugs was evaluated based on fungal eradication and mortality rates. Fungal eradication (resolution) means that a negative culture after the initiation of therapy in whom *Candida* spp. had previously been cultured from blood and urine, cerebrospinal fluid or transtracheal aspirate before antifungal therapy. The fungal eradication rate, fungal eradication time and the duration of anti-fungal therapy in the two groups were compared.

The incidence of renal toxicity, hepatotoxicity, hypokalemia, thrombocytopenia and fever in the two groups were evaluated to determine side effects and safety. The concentrations of creatinine, electrolytes, transaminase levels and urine output were determined before the onset of treatment, 24 h following the last dosage and at peak levels following treatment. The tests were repeated during treatment when deemed necessary. A renal side effect was defined as a 50% increase in the serum creatinine levels from the baseline level (renal toxicity),[13] or oliguria, with urine output less than 1 mL/kg/h. Liver side effects (hepatotoxicity) were defined as a 100% increase in the serum transaminase, particularly alanine aminotransferase (ALT) levels from the baseline level.[13] Hypokalemia was diagnosed when the serum potassium concentration was < 3 mmol/L, and thrombocytopenia was diagnosed when the serum platelet count was $< 100 \times 10^9$/L. A fever was defined as a 6 a.m. oral temperature of > 37.2 ℃ (> 98.9° F) or a 4 - 6 p.m. oral temperature of > 37.7℃ (> 99.9° F).[14] Axillary temperatures were generally 0.4℃ (0.7° F) lower than the oral readings, so a fever was defined as an axillary temperature of > 37.4℃ (≥ 37.5℃) at any time of the day.

Several perinatal and postnatal variables were evaluated to determine factors influencing the treatment outcome. These variables included: gestational age, birth weight, central line insertion, antibiotics use, duration of total parenteral nutrition, length of time on mechanical ventilation, length of hospital stay, gender, RDS, patent ductus arteriosus (PDA) confirmed with echocardiography, high grade intraventricular hemorrhage (IVH, $\geq$ Gr.III), periventricular leukomalacia (PVL), and bronchopulmonary dysplasia (BPD), oxygen dependency at a corrected age of 36 weeks.

The results are presented as the mean ± standard deviation. Statistical analysis was performed using a chi-square test or Fisher's exact test for dichotomous outcome data, and a t-test or Mann-Whitney U test for continuous data. Differences between AmBisome group and Amphotericin group were analyzed. A p value < 0.05 indicated a significant difference.

Table 2. Demographic Data

	AmBisome® group (n = 26)	Amphotericin group (n = 20)	*p* value
Gestational age (week + day)	$26^{+1} \pm 3^{+0}$	$26^{+6} \pm 1^{+4}$	0.322
Birth weight (g)	820 ± 240	901 ± 218	0.265
TPN duration (day)	42 ± 19	51 ± 29	0.349
Mechanical ventilation duration (day)	76 ± 49	50 ± 26	0.067
Hospital stay length (day)	92 ± 49	96 ± 25	0.746
Sex, male	15 (63%)	11 (55%)	0.422
RDS	22 (92%)	16 (80%)	0.248
PDA	20 (83%)	13 (65%)	0.147
NEC	3 (13%)	2 (10%)	0.589
BPD	5 (21%)	3 (15%)	0.461
IVH (≥ Gr III)	2 (8%)	2 (10%)	0.624
PVL	2 (8%)	1 (5%)	0.570

RDS, respiratory distress syndrome; PDA, patent ductus arteriosus confirmed with echocardiography; NEC, necrotizing enterocolitis; BPD, bronchopulmonary dysplasia, defined as an oxygen dependency at the corrected age of 36 weeks; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; TPN, total parenteral nutrition.

RESULTS

Demographic findings (Table 2)

The mean gestational age and birth weight were $26^{+3} \pm 2^{+3}$ weeks and 856 ± 236 g, respectively. The mean gestational age and birth weight for the AmBisome group were $26^{+1} \pm 3^{+0}$ weeks and 820 ± 240 g, respectively, whereas the mean gestational age and birth weight were $26^{+6} \pm 1^{+4}$ weeks and 901 ± 218 g, respectively, for the Amphotericin group. The gestational age, birth weight, duration of time on total parenteral nutrition and mechanical ventilation, as well as the number of days spent in hospital were similar for both groups. A central catheter was inserted in all patients at the time of the diagnosis of systemic candidiasis, and all received antibiotic therapy prior to initiation of antifungal therapy. Table 2 details the demographic characteristics of the study groups.

Efficacy (Table 3)

Table 3 outlines the mean values for treatment duration and drug dosages. The mean number of days necessary for eliminating *Candida* spp. was not significantly different for the two groups (p = 0.712). *Candida* spp. was isolated for 73% (19/26) of the AmBisome group and 90% (18/20) of the Amphotericin group. The remainder was considered clinical candidiasis. Fungal eradication was achieved for 84% (16/19) of the AmBisome group and 89% (16/18) of the Amphotericin group, which was not a significant difference (p = 0.680). The overall mortality rate directly related to systemic candidiasis was 11%, and there was no significant difference between the two groups (p = 0.868). Variability among the centers could not be eliminated, and all three VLBWI, who died as a result of systemic candidiasis in the AmBisome group, were born, admitted and treated at hospitals other than ours. The fungal infection was never eradicated in these patients. One patient was a male born at a gestational age of 28^{+5} weeks and a birth weight of 1280 g. His infection was severe with a serum platelet count of 5×10^9/L before treatment, and the isolated *C. parapsillosis* was never eradicated during treatment. His urine output and serum creatinine levels, however, were within normal limits.

Table 3. Efficacy

	AmBisome® group (n = 26)	Amphotericin group (n = 20)	*p* value
Onset of therapy (day)	23 ± 17	27 ± 16	0.488
Duration of therapy (day)	13 ± 5	20 ± 10	0.004
Starting dose (mg/kg/day)	2.5 ± 2.1	0.3 ± 0.2	
Maximum dose (mg/kg/day)	5.2 ± 1.1	1.5 ± 0.6	
Cumulative dose (mg/kg)	56.7 ± 28.6	24.5 ± 13.8	
Culture positive	19/26 (73%)	18/20 (90%)	0.428
Fungal eradication	16/19 (84%)	16/18 (89%)	0.680
Fungal eradication (day)	9 ± 8	10 ± 9	0.712
Mortality	8/26 (31%)	5/20 (25%)	0.742
Mortality due to fungal infection	3/26 (12%)	2/20 (10%)	0.868

Another patient was born at a gestational age of 24^{+1} weeks and a birth weight of 655 g. In this case, *C. albicans* was isolated and never eradicated. Oliguria was already present, and the serum creatinine level was 2.0 mg/dL prior to treatment. This instance of renal failure may have been due to hemodynamically significant PDA and the indocin treatment. The third patient, a female, was born at 24^{+2} weeks and had a birth weight of 575 g. *C. albicans* was isolated and the patient did not present with hepatotoxicity or renal toxicity, even when the cumulative dose of AmBisome® was 78.0 mg/kg.

Side effects and safety (Table 4)

Urine output did not decrease significantly following treatment and was similar between the study groups (2.3 mL/kg/hr in the AmBisome group vs 2.8 mL/kg/hr in the Amphotericin group, $p = 0.116$), and episodes of oliguria were similar between groups ($p = 0.118$). Serum creatinine levels were similar in the two groups prior to treatment and at the peak level following treatment. The incidence of renal toxicity, defined as a 50% increase in the serum creatinine level, was lower in the AmBisome group with 21% (5/26) incidence and 55% (11/20) incidence for the Amphotericin group ($p = 0.029$).

The ALT level prior to treatment was similar for the two groups, but the peak level following treatment was higher in the Amphotericin group. The incidence of hepatotoxicity, defined as a 100% increase in the serum ALT level, was significantly lower for the AmBisome group (25% in AmBisome group, 65% in Amphotericin group, $p = 0.014$).

Episodes of hypokalemia, thrombocytopenia and fever were similar for both groups ($p = 0.160$, 0.533, 0.086, respectively).

DISCUSSION

These results suggest that AmBisome® is an effective and safe antifungal agent in the treatment of systemic candidiasis in VLBWI. The mean duration of AmBisome® therapy was shorter than amphotericin B therapy, but fungal eradication rates, eradication time, and mortality rates were similar. AmBisome® was administered at a higher daily maximum dose and cumulative dose than amphotericin B, but renal toxicity and hepatotoxicity were significantly lower in the AmBisome group.

Amphotericin B binds to ergosterol, a sterol component unique to fungal cell membranes, altering the cell permeability and causing the leakage of cytoplasmic content (electrolyte loss) that ultimately produces fungal death. Unfortunately, when amphotericin B is infused into

Table 4. Side Effects and Safety

	AmBisome® group (n = 26)	Amphotericin group (n = 20)	*p* value
Oliguria after treatment	4 (17%)	0 (0%)	0.118
Creatinine			
Before treatment (mg/dL)	0.8 ± 0.7	0.7 ± 0.3	0.364
After treatment (mg/dL)	0.9 ± 0.8	1.2 ± 0.6	0.217
50% rise	5 (21%)	11 (55%)	0.029
Aspartate aminotransferase			
Before treatment (U/L)	31 ± 16	28 ± 20	0.666
After treatment (U/L)	62 ± 59	101 ± 75	0.079
100% rise	5 (21%)	11 (55%)	0.029
Alanine aminotransferase			
Before treatment (U/L)	12 ± 13	11 ± 18	0.995
After treatment (U/L)	29 ± 38	63 ± 58	0.033
100% rise	6 (25%)	13 (65%)	0.014
Potassium			
Before treatment (mmol/L)	4.6 ± 0.8	4.4 ± 0.9	0.668
After treatment(mmol/L)	3.9 ± 0.9	3.6 ± 0.8	0.224
Hypokalemia after treatment	1 (4%)	4 (20%)	0.160
Platelet count			
After treatment ($\times 10^9$/L)	108 ± 98	74 ± 71	0.257
Thrombocytopenia	14 (58%)	11 (55%)	0.533
Fever (BT ≥ 37.5℃), no	0 (0%)	3 (15%)	0.086

circulation, it also binds to cholesterol, a sterol component of the mammalian cell membrane, and creates a similar disruption to the cell membrane. Again, the normal cytoplasmic contents leak, causing cell death that results in serious side effects such as renal toxicity.[15] Although there was no detectable hepatic failure or renal failure caused directly by the drug itself, there was significant detectable hepatic toxicity or renal toxicity within the study. New lipid formulated amphotericin B preparations have been developed to reduce renal toxicity levels of amphotericin B and AmBisome® is the only commercially available lipid formulation of amphotericin B containing liposomal structures. AmBisome®, or liposomal amphotericin B, is a very small unilamellar vesicle (< 100 nm in size) with amphotericin B intercalated within the phospholipid bi-layer of the liposome. AmBisome® has a preferential affinity for fungal ergosterol cells over mammalian cholesterol cells. Therefore, once AmBisome® binds to the fungal cell wall, the fungal cell releases phospholipase, which then digests the liposome. This causes amphotericin B, which is intercalated within the liposome, to leave the liposome and disrupt the fungal cell membrane by binding to it. Ultimately, this results in selective fungal cell death with fewer systemic side effects.[16,17]

Lipid formulated amphotericin B has several advantages over conventional amphotericin B, including an increased daily dosage of the parent drug (up to 10-fold), high tissue concentrations in the primary reticuloendothelial organs (lungs, liver, and spleen), a decrease in infusion-related side effects (especially liposomal amphotericin B), and a marked decrease in renal toxicity. AmBisome® concentration was found to be highest in the liver, spleen, kidneys and lungs, and the extent of the tissue distribution of AmBisome® may be an important determinant of the treatment outcome.[18]

The pathophysiology of renal toxicity for amphotericin B, other than non-selectively binding to mammalian cholesterol cells, involves the vasoconstriction of and direct interaction with the renal epithelial cell membranes, resulting in a decrease in GFR and tubular dysfunction. Amphotericin B forms pores in cell membranes causing tubular dysfunction, and is responsible for severe vasoconstriction that decreases renal blood flow and GFR, ultimately causing ischemic injury. Together, these two mechanisms induce acute renal dysfunction. Several papers report the rate of acute renal failure for patients on amphotericin B to be between 49% and 65%.[9] Amphotericin B induces the following changes: hypokalemia, hypomagnesemia, renal tubular acidosis, and increases in serum creatinine preceded by tubular dysfunction. In addition, amphotericin B is responsible for prolonged hospitalization, as well as increased costs and mortality due to hemodialysis caused by amphotericin B induced acute renal failure. Therefore, some studies regard this format of renal toxicity not as a simple, transient episode but a severe disease that should be prevented if at all possible.[19] Scarcella et al.[20] concluded, however, that amphotericin B is well-tolerated in preterm infants. Recently, many specialists have grown to regard the most common side effect of amphotericin B as mild renal toxicity that is resolved after the cessation of therapy.[21] In our study, renal function was evaluated based on urine output and serum creatinine levels. Urine output and episodes of oliguria following treatment were similar between the study groups. Serum creatinine levels were similar for both groups, not only before treatment but also at the peak level following treatment. Additionally, renal toxicity, defined as a 50% increase in the serum creatinine level, was lower in the AmBisome group following treatment.

The ALT level before the onset of treatment was similar for both groups, but the peak level following treatment was higher in the Amphotericin group. The incidence of hepatotoxicity, defined as a 100% increase in the serum ALT level, was significantly lower in the AmBisome group. Drug-induced hepatotoxicity usually presents symptoms of acute hepatocellular injury, cholestasis, or both. Generally, in hepatocellular disorders, ALT concentration is elevated, and in cholestatic injury, bilirubin and alkaline phosphatase concentrations may or may not be elevated. A case report describes the hepatotoxicity with amphotericin B in an adult patient.[22] A 53-year-old woman with a non-small cell lung cancer received amphotericin B, and on the next day, her bilirubin, aspartate aminotransferase (AST), and ALT levels had increased markedly. These levels were normalized after discontinuing amphotericin B and AmBisome® was then administered. Following AmBisome administration, bilirubin levels increased mildly, but the AST and ALT were unaffected. The bilirubin level normalized following discontinuation of the drug. However, the mechanism of hepatotoxicity induced by amphotericin B was not determined in this study. Mohan and Bush[23] (2002) reported the first case of amphotericin B induced hepatotoxicity in children. The patient was a 9-year-old girl with cystic fibrosis who had developed fulminant renal and hepatic dysfunction after a short course of intravenous amphotericin B for a suspected aspergillus infection, even though she did not have clinical evidence of invasive aspergillosis. The patient's maximum AST and ALT levels were up to 1112 U/L and 364 U/L, respectively. Her AST and ALT improved gradually after discontinuing the amphotericin B and normalized after a seven-day period. Juster-Reicher et al.[1] reported a transient increase in the serum bilirubin and hepatic transaminases levels in one infant after administering AmBisome® in 24 VLBWI, all weighing less than 1500 g. They could not explain the mechanism of AmBisome®-induced hepatotoxicity. Some researchers[23] have reported that the non-selective disruption of mammalian cells due to cholesterol binding is the mechanism for the toxic effects of amphotericin B, but the precise mechanism of hepatotoxicity is unknown despite several case reports of amphotericin B and AmBisome®-associated hepatotoxicity.

In one study, a comparison of amphotericin B therapy (n = 34) and AmBisome® therapy (n = 6) in VLBWI weighing less than 1500 g[24] concluded that the fungal eradication time was five days for the AmBisome group, and eight days for the Amphotericin group. In addition, the fungal eradication rate was 83% in the AmBisome group,

and 68% in the Amphotericin group. Mortality due to the fungal infection was 16.7% and 14.7%, respectively. In this study, the number of VLBWI assigned to the AmBisome group (n = 26) was higher than that reported by Linder et al. (n = 6),[24] the fungal eradication rate was higher (84% in AmBisome group, 89% in Amphotericin group), and the mortality was lower (12% in AmBisome group, 10% in Amphotericin group). Scarcella et al.[20] administered liposomal amphotericin B to 40 preterm neonates with a severe fungal infection. The dose ranged from 1 mg/kg/day to a maximum of 5 mg/day based on the clinical response. Fungal eradication was observed in 70% (28/40) of the patients.

In conclusion, AmBisome® is an effective and safe antifungal agent for the treatment of systemic candidiasis in VLBWI weighing less than 1500 g.

REFERENCES

1. Juster-Reicher A, Leibovitz E, Linder N, Amitay M, Flidel-Rimon O, Even-Tov S, et al. Liposomal amphotericin B (AmBisome) in the treatment of neonatal candidiasis in very low birth weight infants. Infection 2000;28:223-6.
2. Rodriguez D, Almirante B, Park BJ, Cuenca-Estrella M, Planes AM, Sanchez F, et al. Candidemia in neonatal intensive care units: Barcelona, Spain. Pediatr Infect Dis J 2006;25:224-9.
3. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics 2002;110:285-91.
4. Fridkin SK, Kaufman D, Edwards JR, Shetty S, Horan T. Changing incidence of Candida bloodstream infections among NICU patients in the United States: 1995-2004. Pediatrics 2006;117:1680-7.
5. Adler A, Litmanovitz I, Regev R, Arnon S, Bauer S, Dolfin T. Breakthrough candida infection in a preterm infant with congenital cutaneous Candida albicans infection. Am J Perinatol 2005;22:169-72.
6. Kossoff EH, Buescher ES, Karlowicz MG. Candidemia in a neonatal intensive care unit: trends during fifteen years and clinical features of 111 cases. Pediatr Infect Dis J 1998;17:504-8.
7. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, et al. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. Pediatrics 2006;117:84-92.
8. Goldman RD, Koren G. Amphotericin B nephrotoxicity in children. J Pediatr Hematol Oncol 2004;26:421-6.
9. Deray G. Amphotericin B nephrotoxicity. J Antimicrob Chemother 2002;49 Suppl 1:37-41.
10. Cuzzolin L, Fanos V, Pinna B, di Marzio M, Perin M, Tramontozzi P, et al. Postnatal renal function in preterm newborns: a role of diseases, drugs and therapeutic interventions. Pediatr Nephrol 2006;21:931-8.
11. Bueva A, Guignard JP. Renal function in preterm neonates. Pediatr Res 1994;36:572-7.
12. Dismukes WE. Introduction to antifungal drugs. Clin Infect Dis 2000;30:653-7.
13. Cetin H, Yalaz M, Akisu M, Hilmioglu S, Metin D, Kultursay N. The efficacy of two different lipid-based amphotericin B in neonatal Candida septicemia. Pediatr Int 2005;47:676-80.
14. Charles A. Dinarello, Jeffrey A. Gelfand. Fever and Hyperthermia. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005. p.104-8.
15. Weitkamp JH, Poets CF, Sievers R, Musswessels E, Groneck P, Thomas P, et al. Candida infection in very low birth-weight infants: outcome and nephrotoxicity of treatment with liposomal amphotericin B (AmBisome). Infection 1998;26:11-5.
16. Juster-Reicher A, Flidel-Rimon O, Amitay M, Even-Tov S, Shinwell E, Leibovitz E. High-dose liposomal amphotericin B in the therapy of systemic candidiasis in neonates. Eur J Clin Microbiol Infect Dis 2003;22:603-7.
17. Adler-Moore J, Proffitt RT. AmBisome: liposomal formulation, structure, mechanism of action and preclinical experience. J Antimicrob Chemother 2002;49 Suppl 1:21-30.
18. Wong-Beringer A, Jacobs RA, Guglielmo BJ. Lipid formulations of amphotericin B: clinical efficacy and toxicities. Clin Infect Dis 1998;27:603-18.
19. Baley JE, Kliegman RM, Fanaroff AA. Disseminated fungal infections in very low-birth-weight infants: therapeutic toxicity. Pediatrics 1984;73:153-7.
20. Scarcella A, Pasquariello MB, Giugliano B, Vendemmia M, de Lucia A. Liposomal amphotericin B treatment for neonatal fungal infections. Pediatr Infect Dis J 1998;17:146-8.
21. Bliss JM, Wellington M, Gigliotti F. Antifungal pharmacotherapy for neonatal candidiasis. Semin Perinatol 2003;27:365-74.
22. Olin JL, Spooner LM. Amphotericin B-associated hyperbilirubinemia: case report and review of the literature. Pharmacotherapy 2006;26:1011-7.
23. Mohan UR, Bush A. Amphotericin B-induced hepatorenal failure in cystic fibrosis. Pediatr Pulmonol 2002;33:497-500.
24. Linder N, Klinger G, Shalit I, Levy I, Ashkenazi S, Haski G, et al. Treatment of candidaemia in premature infants: comparison of three amphotericin B preparations. J Antimicrob Chemother 2003;52:663-7.