Liposomal amphotericin B does not induce nephrotoxicity or renal function impairment in premature neonates

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1. Introduction

Despite a large inter-centre variability in their frequencies, Systemic Fungal Infections (SFI) mainly caused by Candida spp. are an increasingly common feature in most NICUs worldwide affecting up to 15% of extremely low birth weight (ELBW) neonates [1,2]. SFI have high morbidity and attributable mortality, and are frequently associated with late neurodevelopmental impairment [3]. 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 [4]. Early treatment when diagnosing or even suspecting a SFI is however imperative due to the devastating severity of a misdiagnosed fungal sepsis.

Antifungal systemic drugs are routinely administered in NICU to preterm infants <1500 g at birth (very low birth weight, VLBW) for treatment of systemic fungal episodes [5], and a liposomal derivative of amphotericin B (liposomal...
amphotericin B, LAMB) is one of the most frequently used antifungal treatments in neonates because of its fungicidal effects.

Amphotericin B belongs to the class of polyene antibiotics, which are characterised by lipophilic and hydrophilic regions. Free amphotericin B 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 with electrolyte disturbances is an undesirable side effect of amphotericin B therapy [6]. Additional adverse effects related to this drug include also infusion reactions with haemodynamic and temperature instability, and thrombocytopenia [7,8]. In addition, the previous or concomitant use of nephrotoxic drugs (e.g. antibiotics, and nonsteroidal anti-inflammatory drugs) might increase the incidence of amphotericin B nephrotoxicity.

Efforts to reduce these side effects have led to the development of amphotericin-lipid formulations, and it has been speculated that these formulations have lesser toxicity. However, studies exploring the effect of LAMB on the renal function in large series of preterm neonates are not available. Therefore, concerns have been raised about possible adverse reactions with LAMB therapy, and often contribute to hesitation in beginning empiric treatment before positive culture findings are obtained.

The purpose of this study was to assess the adverse renal effects of LAMB administered to a large series of VLBW infants affected by SFI.

2. Material and methods

2.1. Study design and setting

This retrospective study was performed by reviewing the clinical records of all VLBW neonates admitted to our NICU in the period from 1.1.98 to 31.12.07.

All those undergoing any form of treatment with LAMB during their NICU stay, both because of a diagnosed SFI and as an empirical treatment, were identified and considered eligible for the study.

The study was conducted at the Sant’Anna Hospital, Turin, Italy. This is a level III Unit in the greater Turin area (1,500,000 inhabitants and 15,000 births per year) with a mean delivery rate of 4000 per year and 500 admissions to its NICU.

The exclusion criteria were:
- incomplete data or charts;
- incorrect administration of the antifungal drug (i.e. incorrect dosage);
- prophylactic, but not therapeutic, administration of the antifungal drug;
- death prior to the 3rd day of life (DOL 3).

The demographic, gestational and perinatal data of the eligible neonates were examined. Antenatal risk factors were also evaluated, specifically those associated with maternal nutrition, maternal diabetes, septic episodes, clinical, microbiological-culture results, laboratory data, treatments and outcome). In details, 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, type of Candida species isolated, infection site, number of positive cultures, and time to achieve negative cultures.

A number of causes that might have affected the frequency or relative weight of factors increasing or decreasing the risk of SFI and subsequent increased or decreased frequency of LAMB use were ruled out. In details, the infection control policies were not significantly different in our Unit nor in the hospital as a whole over the period, and followed the criteria expressed in protocols produced and regularly checked by a dedicated Control of Nosocomial Infections Committee. In addition, the quarterly Surveillance Reports issued by this Committee never disclosed either an increase of fungal isolates that might have been related to problems in infection control, nor any episodic increase in C. parapsilosis isolates (often related to the spread of hospital-acquired fungal infections). Finally, no changes occurred in the policies and protocols regarding the use of antenatal and neonatal antibiotics or steroids or neonatal H2-antagonists, nor in nutritional protocols and policy.

2.2. Fungal colonisation and infection surveillance – definition of systemic fungal infection (SFI)

As a routine policy, systematic surveillance for detection of fungal colonisation was performed through clinical and weekly surveillance cultures. The following surveillance cultures were performed: ear canal swab, umbilical catheter at birth; stool, gastric aspirate, rectal swab, or pharyngeal swab: at least 3 of them weekly during the stay in NICU. In addition, cultures were obtained from surgical devices after removal, and from any sites indicated by the physician.

A microbiologically documented (proven) fungal infection was defined as occurring ≥4 days after birth and included clinical signs and symptoms consistent with sepsis together with isolation of a fungal causative organism from (1) blood (drawn from peripheral sites), or (2) urine (collected by suprapubic puncture or sterile bladder catheterisation (with growth of more than 10,000 fungal organisms/ml), or (3) cerebrospinal, or (4) peritoneal fluid.

Isolation of fungi from specimens other than those listed above was considered as colonisation. Fungal colonisation was defined as the detection of at least 1 culture positive for fungi during the stay in NICU. When a fungal isolate was retrieved from urine collected with non-sterile procedures (i.e. by means of urine bags or indwelling catheters), or with growth of less than 10,000 fungal organisms/ml, this was considered as fungal colonisation of urine, and not as urinary infection.

SFI-related death was defined as death within 3 days after the last positive culture from any site without other causes, or isolation of fungal pathogens at autopsy.

These criteria conform to the guidelines in international consensus documents [9–11] and the recommendations of the Italian Neonatology Society’s Fungal Infections Task Force [12].

2.3. Unit’s policy on antifungal prophylaxis with fluconazole

We have previously reported that since January 2001, as a Unit’s policy, all VLBW infants admitted to our Unit receive prophylactic fluconazole [13]. The regimen is 6 mg/kg fluconazole (DIFLUCAN; Pfizer Italia s.r.l.; Latina/Roma; Italy) every 72 h in the first week of life, then every 48 h from the second week until DOL 30 for neonates with birth weight >1000 <1500 g and DOL 45 for ELBW neonates, or until earlier discharge, or until the need for systemic antifungal therapy (liposomal amphotericine B is the first choice) due to the onset of SFI. This schedule was partially modified during a 15-month period between 2004 and 2005, when approximately one third of the VLBW neonates received 3 mg/kg and another one third did not receive fluconazole: this was due to the involvement of our NICU in a multicentre trial on fluconazole performed with a NICU network in Italy. Fluconazole is administered starting from
DOL 1 as a single dose i.v. or orally, depending on the availability of a venous line and/or on the tolerance of oral feeding. As expected, the prophylactic use of fluconazole has led to a steady decline of the therapeutic use of this azole since 2001.

2.4. Treatment of confirmed or suspected/presumed SFI

During the study period, our protocol for treatment of SFI was to initiate LAMB (AmBiSome, Gilead, Foster City, CA USA) therapy with a dose of 1.5 mg/kg. If the patient tolerated the first dose, then the LAMB dose was gradually increased by 0.5 mg/kg per day to a maximal dose of 5 mg/kg per day for the duration of treatment. The length of LAMB therapy, the time to reach 5 mg/kg per day, the dose of LAMB used until renal compromise occurred, and the cumulative total dose were recorded. We also examined the use of potentially nephrotoxic drugs (gentamicin, tobramycin, vancomycin, ibuprofen and indomethacin) before and during LAMB therapy.

When SFI was presumed in a neonate undergoing prophylactic fluconazole, this agent was suspended and systemic antifungal therapy with drug(s) other than fluconazole was given empirically until the culture results were known.

When an episode of SFI was diagnosed, removal of indwelling venous catheter(s) was the standard policy for the management of central intravascular lines. Infants were treated with antifungal drugs for a minimum of 7 days after the first persistent negative culture.

2.5. Renal toxicity surveillance

The occurrence of potential LAMB-induced nephrotoxicity was 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, as well as urine output and blood pressure data, are routinely collected during NICU stay as a part of the daily routine neonatal care. For the present study, we considered the data starting from 3 days before the initiation of LAMB 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 week, and twice weekly thereafter. Fluid and electrolyte management was at the discretion of the attending physician.

LAMB-induced renal compromise was defined by the presence of at least one among the following:
1. an increase in serum creatinine levels of >1 mg/dl or >50%;
2. urine output <1 mL/kg per hour;
3. decrease in urine output of 50%;
4. hypokalaemia was defined as a serum potassium concentration <3 mEq/dl.

Fluid, urine volumes, laboratory and electrolyte data were analysed for 3 time periods: 3 days prior to LAMB therapy, first 5 days after the initiation of LAMB therapy, and days 6 to 15 after the initiation of LAMB therapy. These periods were selected on the basis of the current literature data, which suggest that compromise in the preterm neonates treated with systemic antifungal drugs develops by a mean of 5 days and resolves within a mean of 10 days after the initiation of antifungal therapy with amphotericin B and its derivatives. As amphotericin B may blunt erythropoiesis, data on the occurrence of anaemia requiring transfusion and of severe thrombocytopenia (<50,000 platelets/mm³) were also retrieved and analysed.

2.6. Statistical analysis

The demographic and clinical data were examined and reported as mean ± SD. The continuous data with normal distribution were compared by using Student’s t test. The ordinal data were compared by using Fisher’s exact test.

Serum creatinine, serum potassium and urine volume output were evaluated for the different periods using ANOVA for repeated measures. Significance was accepted at P < 0.05.

All computations were made by using the SPSS software, version 9.0.

3. Results

During the study period, 865 infants were admitted to our NICU and survived more than 3 days. Seventy-two were discarded due to incomplete data or charts (n = 65), and incorrect/not adherent to protocols administration of the antifungal drug (n = 7).

Antifungal treatment with LAMB was performed in 71 (8.9%) of the remaining 792 neonates. Their demographics, clinical, management, colonisation and outcome characteristics are illustrated in Table 1, as well as their renal function parameters during and after the treatment with LAMB.

Thirteen patients had been treated with prophylactic fluconazole prior to the initiation of LAMB. Five infants received Flucytosine in addition to LAMB, and two Fluconazole. All these neonates remained included in the study.

LAMB was administered on the basis of a proven systemic infectious episode in 55 cases, and as empiric treatment in 16 cases. No neonate underwent more than one single course of LAMB.

The 55 episodes of proven SFI occurred at a median age of 18 (± 9) days, and were caused by C. albicans (45 cases), C. parapsilosis (8 cases), C. glabrata (4 cases), C. krusei (2 cases), Aspergillus fumigatus, C. tropicalis and C. guilliermondii (1 case each). Seven neonates were infected by 2 species: in four cases C. albicans + C. parapsilosis, in one C. albicans + C. krusei, in one C. parapsilosis + C. tropicalis, in one C. albicans + C. glabrata.

The breakdown of SFI cases was as follows: 40 bloodstream infections, 10 urinary tract infections, 4 meningitis, and 1 detected at autopsy.

End-organ damage was documented in 8 infants (1 with fungal ball identified with renal ultrasonography; 3 with ophthalmic evidence of fungus; 1 with cardiac vegetation; 1 with cerebral abscesses; 4 with hepato-splenic candidiasis).

The mean duration of treatment with LAMB was 14 (±9) days; in infants treated for proven SFI it was 18 (±11), and in those treated for presumed SFI it was 12 (±8) days, respectively.

The mean cumulative dose administered was 58 (±25) mg/kg per infant (73 (±36) mg/kg in proven, and 50 (±20) mg/kg in presumed SFI, respectively).

Renal compromise, defined according to the criteria above mentioned, occurred in 2 out of 71 (2.8%) septic, treated patients. In the same historical period, renal compromise occurred in 18 of 721 VLBW infants not treated with LAMB (2.4%; p = 0.80).

In the LAMB-treated infants, the onset of renal compromise was documented in the fifth and in the sixth day after the initiation of LAMB, respectively. In the first case, an elevation of creatinine levels to 1.35 mg/dl was documented; in the second, oliguria (urine output <1 mL/kg per hour) was recorded for a 18-hour interval, requiring treatment with furosemide. In both patients LAMB was withdrawn and antifungal therapy was continued with use of fluconazole at a 10 mg/kg/day dosage. Renal compromise lasted for a period of 3 and 4 days, respectively, and resolved on day 8 and 10 after initiation of
Table 1
Demographics, clinical, management, outcome characteristics, and renal function parameters during and after the treatment with LAMB compared to all other VLBW infants

<table>
<thead>
<tr>
<th>Demographics, clinical, management, outcome characteristics</th>
<th>VLBW infants</th>
<th>LAMB treated (n=71)</th>
<th>Not LAMB treated (n=721)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g), mean±SD</td>
<td></td>
<td>1005±261</td>
<td>1175±288</td>
<td>0.01</td>
</tr>
<tr>
<td>Gestational age (wks), mean±SD</td>
<td></td>
<td>29.0±2.9</td>
<td>30.3±2.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Maternal preeclampsia</td>
<td></td>
<td>15%</td>
<td>23%</td>
<td>0.10</td>
</tr>
<tr>
<td>Apgar score at 5 min, mean±SD</td>
<td></td>
<td>6±2</td>
<td>6±2</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Prior fluconazole prophylaxis</td>
<td></td>
<td>15%</td>
<td>44.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Use of 3rd generation cephalosporins</td>
<td></td>
<td>35%</td>
<td>22%</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of postnatal steroids</td>
<td></td>
<td>25%</td>
<td>21%</td>
<td>0.45</td>
</tr>
<tr>
<td>Use of vancomycin</td>
<td></td>
<td>28%</td>
<td>18%</td>
<td>0.09</td>
</tr>
<tr>
<td>Antibiotic therapy, excluding aminoglycosides (total duration in days), mean±SD</td>
<td></td>
<td>14±11</td>
<td>12±13</td>
<td>0.29</td>
</tr>
<tr>
<td>Duration of aminoglycosides (days)</td>
<td></td>
<td>5±4</td>
<td>5±4</td>
<td>0.99</td>
</tr>
<tr>
<td>Use of TPN</td>
<td></td>
<td>60%</td>
<td>42%</td>
<td>0.12</td>
</tr>
<tr>
<td>Days on supplemental oxygen</td>
<td></td>
<td>19±11</td>
<td>15±11</td>
<td>0.15</td>
</tr>
<tr>
<td>Endotracheal intubation</td>
<td></td>
<td>88%</td>
<td>70%</td>
<td>0.04</td>
</tr>
<tr>
<td>Central venous line(s) positioned</td>
<td></td>
<td>78%</td>
<td>65%</td>
<td>0.15</td>
</tr>
<tr>
<td>Major surgeries</td>
<td></td>
<td>7%</td>
<td>10%</td>
<td>0.40</td>
</tr>
<tr>
<td>Thrombocytopenia, &lt;50,000/mm³</td>
<td></td>
<td>5%</td>
<td>3%</td>
<td>0.65</td>
</tr>
<tr>
<td>Number of red blood cells transfusions, mean±SD</td>
<td></td>
<td>2.2±1.1</td>
<td>1.8±1.2</td>
<td>0.35</td>
</tr>
<tr>
<td>Duration of stay in NICU (days), mean±SD</td>
<td></td>
<td>38±28</td>
<td>30±32</td>
<td>0.01</td>
</tr>
<tr>
<td>Overall mortality</td>
<td></td>
<td>21.2%</td>
<td>9.4%</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>SFI, LAMB treatment and Renal function parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at fungal sepsis diagnosis and initiation of LAMB therapy (DOL), mean±SD</td>
<td></td>
<td>18±9</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Total length of therapy (days), mean±SD</td>
<td></td>
<td>14±9</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Total cumulative LAMB dose (mg/kg), mean±SD</td>
<td></td>
<td>58±25</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine values (mg/dl), mean±SD</td>
<td></td>
<td></td>
<td></td>
<td>p=0.18*</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.55±0.2</td>
<td>0.48±0.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5 days of LAMB</td>
<td>0.74±0.3</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–15 days of LAMB</td>
<td>0.83±0.4</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum potassium values (mEq/dl), mean±SD</td>
<td></td>
<td></td>
<td></td>
<td>p=0.25*</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.3±3</td>
<td>5.1±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5 days of LAMB</td>
<td>4.9±3</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–15 days of LAMB</td>
<td>4.5±3</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily urine output (ml/kg/day), mean±SD</td>
<td></td>
<td></td>
<td></td>
<td>p=0.33*</td>
</tr>
<tr>
<td>Baseline</td>
<td>105 (±45)</td>
<td>115 (±50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–5 days of LAMB</td>
<td>88±35</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–15 days of LAMB</td>
<td>75±45</td>
<td>Not applicable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal compromise</td>
<td>2/71 (2.8%)</td>
<td>18/721 (2.4%)</td>
<td></td>
<td>0.80</td>
</tr>
<tr>
<td>LAMB dose at renal compromise, mg/kg</td>
<td></td>
<td>2.5 (1st case)</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Concomitant nephrotoxic drugs</td>
<td></td>
<td>yes</td>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Concomitant antibiotics</td>
<td></td>
<td>no</td>
<td>Not applicable</td>
<td></td>
</tr>
</tbody>
</table>

Values represent mean ± SD, or number of cases.
*p-value paired t-test versus Baseline mean.

LAMB therapy. Both neonates had a proven case of SFI, with isolation of *C. albicans* from blood, and no documented end-organ damage attributable to the SFI. Both recovered from this SFI episode and were discharged without any ongoing renal complication.

In the remaining 69 LAMB-treated patients, no significant alterations in the renal function parameters were documented when comparing the days before and after initiation of LAMB. The mean daily serum creatinine concentrations showed a trend toward a slight nonsignificant increase, and the serum
values never achieved the 1 mg/dl cut-off. The increase in serum creatinine levels occurred at 3 ± 2 mean days after initiation of LAMB. No increase in serum creatinine concentrations of >50% was ever documented.

The overall in-hospital mortality was 21.2% in the infected neonates compared to 9.4% in the neonates not infected by fungi admitted to our NICU in the same period. Five *Candida*-attributable deaths occurred. Overall mortality was significantly (p = 0.04) lower in the neonates who had received prior fluconazole prophylaxis (15% vs. 23.0%, respectively).

### 4. Discussion

VLBW infants are at high risk of developing systemic fungal infections. Host factors such as immaturity of the immune system and prolonged use of antibiotics make such infants more vulnerable [1–4], and frequently in need of courses of antifungal systemic drugs due to proven or suspected episodes of fungal sepsis.

The main finding of this retrospective study is that LAMB used to treat preterm VLBW neonates with proven or suspected fungal sepsis was well tolerated and did not induce nephrotoxicity in the large majority of cases.

As previously mentioned, amphotericin B is a polyeene characterised by lipophilic and hydrophilic regions, and by the ability to bind to the cholesterol in renal tubular cells thus potentially causing renal damage [6]. Two strategies have been demonstrated to ameliorate amphotericin B-induced renal toxicity, i.e., incorporation into a liposomal amphotericin system [14–19] and salt loading before amphotericin B administration [8,20]. In literature, there is uncertainty on the safety of such drugs, and the data currently available have been obtained mainly from case report series and retrospective studies in adult patients. In settings other than premature neonates, anyhow, some clinical trials have demonstrated decreased amphotericin B-induced nephrotoxicity with the use of the liposomal formulation, whereas other controlled clinical trials have failed to demonstrate improved outcomes or decreased mortality rates, compared with conventional amphotericin B [21–23].

In this view, our retrospective study adds to the scattered reports of absence of LAMB toxicity in literature in the last decade [15,24,25].

Although in our report only 55 of 71 treated patients had a proven systemic fungal infection, the present paper provides data from the most numerous neonatal case series in literature to date, showing evidence that LAMB may substantially be considered a safe treatment for systemic candidiasis in preterm neonates in NICU.

Only two out of seventy-one treated infants, in fact, showed evidence of renal compromise: however, the dysfunction was only transient and reversible, as both infants recovered and were discharged without ongoing renal failure. In these two cases, we kept a prudent attitude and decided to discontinue LAMB despite the alteration of the renal function values was only mild. Such decision was justified by the availability of cultures indicating full sensitivity of the fungal isolates (*C. albicans* in both cases) to fluconazole, a drug that has a lesser, if any, impact on the kidney and that may be the second choice in case of suspected nephrotoxicity of LAMB. This strategy proved effective, as both infants recovered from renal compromise none-the-less continuing a systemic antifungal treatment until recovery from the fungal sepsis and eradication of the fungi from the cultures.

In all treated infants, the mean serum values of creatinine and potassium showed a trend towards increasing and decreasing, respectively, over the days of treatment. Similarly, the daily urine output had a trend to decrease during the treatment. Although these trends were far from statistical significance, they suggest that some form of renal toxicity may exist and that a high focus on the renal function monitoring has to be maintained during the treatment. Possibly, such modifications in the renal function values might be related to the severity of the concomitant systemic fungal disease rather than to the therapy itself, as in most cases infants treated with LAMB were critically ill due to a life-threatening underlying condition such as sepsis.

Clinical data from adults and animals have indicated that adequate hydration is important for the prevention of amphotericin B-induced nephrotoxicity [26]. The mean age at fungal sepsis diagnosis and initiation of LAMB therapy in our series was 18 (±9) days of life. Noteworthy, at this age preterm neonates usually do not experience a severe fluid depletion, as this usually occurs in the first days of life when there are high transdermal water loss, physiological impairment of the renal function together with an increased catabolism and weight loss. In this view, it appears unlikely that fluid depletion played a role in predisposing our VLBW infants to renal compromise during their 3rd week of life, i.e. when the SFI was diagnosed. On the contrary, such possibility might be strongly considered when facing an episode of SFI that occurs very early in life, like it might happen in case of perinatal candidal infection (mostly caused by vertical transmission of the fungus).

Limitations of our study include the fact that LAMB-induced, long-term nephrotoxicity cannot be excluded. It is known that even transient acute renal failure can inhibit post-natal glomerulogenesis in extremely preterm infants [27], thus long-term follow-up for renal function might be warranted to rule out late renal damage in adult age.

In conclusion, our data from a large case series of preterm VLBW infants treated with LAMB suggest that this antifungal drug is well tolerated and has a minimal impact on global renal function. However, a cautious attitude towards the management of this drug, the implementation of general measures to prevent or minimise its nephrotoxic effects (e.g. maintenance of adequate hydration and sodium intake), and close monitoring of renal function are mandatory until larger, prospective studies on VLBW infants are available.

### Conflict of interest statement

The authors have no financial relationships pertinent to this study to disclose.

### References


