Amphotericin B - Liposomal
Newborn Use Only

2017

Alert	The Antimicrobial Stewardship Team has listed this drug under the following category: Restricted. Amphotericin B is available in 4 forms: Amphotericin B -conventional, Amphotericin B - liposomal, Amphotericin B (phospho)lipid complex and Amphotericin B colloidal dispersion (also known as Amphotericin B Cholesteryl Sulfate Complex). Confusion between these products has led to fatal overdose as well as subtherapeutic dosing.[1] Clinicians should liaise with local ID specialists when treating systemic fungal infections.
Indication	Treatment of invasive fungal infections by susceptible fungi including *Candida spp., Aspergillus spp.* and *Cryptococcus* species.[2,3] *Candida lusitaniae* and *A. terreus* are resistant.
Action	Fungicidal agent which works by binding with a cytoplasmic membrane ergosterol on the organism's surface, causing cell death by increasing cell membrane permeability.[4]
Drug Type	Polyene antifungal
Trade Name	AmBisome
Presentation	Vial contains amphotericin BP equivalent to 50 mg of amphotericin B.[5]
Dosage/Interval	3 mg/kg/dose daily.[6]
Route	Intravenous (IV)
Maximum Daily Dose	7 mg/kg/day.[7]
Preparation/Dilution	Add 12 mL of water for injection to the 50 mg vial for reconstitution to make a concentration of 4 mg/mL. Shake the vial vigorously for at least 30 seconds to disperse completely. Use the 5 micrometre filter supplied to add 4 mL of this solution (= 16 mg) to 4 mL of 5% glucose to make a final volume of 8 mL with a concentration of 2 mg/mL solution.[3,5]
Administration	IV infusion over 60 minutes.[3] **IV line must be flushed with 5% glucose before and after the dose.** In-line filters must have a port diameter of at least 1 micrometre. **Do not mix with any medications.**
Monitoring	Urine output. Full blood count (FBC) for anaemia and thrombocytopenia Renal function (for elevated creatinine), electrolytes (for hypokalaemia) and liver function (for derangements of liver enzymes). Monitor serum concentrations of concomitant nephrotoxic drugs.
Contraindications	Known hypersensitivity to amphotericin B.
Precautions	Administer under close clinical supervision during the initial dosing. Anaphylaxis and respiratory distress have been reported in adults (though not in neonates).
Drug Interactions	Increased risk of nephrotoxicity if used concurrently with other nephrotoxic drugs (even though the liposomal preparation is safer than **conventional** amphotericin B in this regard) e.g. aminoglycosides, vancomycin. Monitor renal function and relevant drug concentrations closely. Adequate clinical studies of the use of the combination of flucytosine with AmBisome have not been conducted. Whilst synergy between flucytosine and amphotericin has been reported, amphotericin B may enhance the toxicity of flucytosine by increasing its cellular uptake and impeding its renal excretion.[3] Corticosteroids and diuretics: May enhance the hypokalaemic effect of amphotericin B.
Adverse Reactions	Electrolyte derangements: Hypokalaemia, hypomagnesaemia, hyperkalaemia, hypocalcaemia. Renal: Elevated urea and creatinine, nephrogenic diabetes insipidus. Haematological: Anaemia, **leucopenia**, thrombocytopenia. Thrombophlebitis at the injection site. Gastrointestinal: Diarrhoea, vomiting, elevated liver enzymes. Infusion-related reactions: Fever, hypotension (rare in neonates). Skin rashes. Tachyarrhythmias, hypotension, hypertension and respiratory distress have been reported in adults.
Compatibility	Fluids: Glucose 5%. Y site: Zidovudine.
Incompatibility	**Fluids:** Sodium chloride 0.9%, Amino acid/glucose solution, lipid emulsion.

	Y Site: Not compatible with any medications commonly used in newborns. **Do not mix with any medications.**
Stability	Reconstituted and diluted solution: Stable for up to 24 hours at 2–8 degrees Celsius.
Storage	Vial: Store below 25 degrees Celsius. Do not freeze. Reconstituted solution: Stable for 24 hours at 2–8°C. Discard unused portion after 24 hours. Do not use the reconstituted solution or infusion if cloudy or a precipitate is present. Protect from light.
Special Comments	If infusion-related immediate reactions occur (e.g. fever, hypotension), duration of infusion may be increased to 3–4 hours. Liposomal amphotericin B is considered to be at a lower risk of causing harm if extravasated (as compared to amphotericin B – conventional).[17] If total parenteral nutrition (TPN) or IV fluids are turned off during the infusion, consider monitoring of blood glucose. Cerebrospinal fluid (CSF) penetration of lipid formulations of amphotericin B is poor.[8,9] Therefore, in cases of fungal meningitis, additional antifungal therapy is required. Even though a neonatal pharmacokinetic study[8] using amphotericin B - lipid complex showed substantial drug concentration in urine, a recent review[2] suggests that the liposomal preparation of amphotericin B is a poor candidate for the treatment of neonatal candiduria as it has lesser renal tissue penetration. This reduced penetration is considered to be responsible for its reduced nephrotoxicity as compared to conventional amphotericin B. Although amphotericin B formulations are known to cause nephrotoxicity and may cause hepatotoxicity, reducing the dose in these disease states is not currently recommended.[19] If nephrotoxicity or hepatotoxicity is a significant concern, consider other antifungals.
Evidence summary	**Efficacy** There are no adequately powered comparative trials of different antifungal therapies for invasive fungal infection in the neonatal setting.[10,11] One small study (24 newborn infants) that compared conventional (not liposomal) amphotericin B with fluconazole found fluconazole to have fewer side effects.[12] Australian 2014 consensus guidelines[6] on antifungal therapy for systemic fungal infections state that (1) the incidence of candidaemia in Australia (2001–2004) was about 1.81 cases per 100 000 population. *Candida albicans* accounted for approximately 50% of invasive *Candida* isolates, followed by *C. parapsilosis* (20%), *C. glabrata* (15%), *C. tropicalis* (5%), *C. krusei* (4%) and *C. dubliniensis* (2%). In the NICU, *C. albicans* and *C. parapsilosis* predominate, (2) all major *Candida* species are usually susceptible to Amphotericin B; *C. glabrata* and *C. parapsilosis* have reduced susceptibility to fluconazole compared to *C. albicans,* however, fluconazole can usually be used successfully if higher doses are used i.e. 10–12 mg/kg/day. *Pichia kudriavzevii* (formerly *C. krusei*) is intrinsically resistant to fluconazole, (3) primary resistance of *Cryptococcus* to antifungal drugs in Australia is uncommon. Amphotericin B is used in combination therapy during the induction phase, (4) there are no prospective data on the optimal duration of therapy for invasive fungal infections and recommendations are largely based on expert opinion. For candidaemia with deep-tissue infection, treatment with systemic antifungal agents for 14 days following the last, positive, sterile-site culture and resolution of clinical features of infection is recommended (LOEIII, GOR C). Similar duration is recommended for peritonitis, but 6 weeks or longer for difficult-to-treat deep foci such as endocarditis, endophthalmitis, mediastinitis or osteomyelitis (GOR D). **Dosage** Australian 2014 Consensus recommendations on Amphotericin B - Liposomal: 3 mg/kg/dose daily.[6] In a retrospective study[13], Weitkamp et al collected data on 21 very low birth weight (VLBW) infants who received liposomal amphotericin B [median dose 2.6 mg/kg/day (range 1–5 mg/kg/day) and median duration: 28 days]. All patients treated with liposomal amphotericin B eradicated fungi and recovered clinically. There was no nephrotoxicity noted. Liposomal amphotericin B (2.5–7 mg/kg/day) was used in 24 VLBW infants with systemic candidiasis in a prospective study.[14] Fungal eradication was achieved in 92% of the episodes with a mean duration

of therapy until the eradication being 9 days. Four of the infants died and in 2 of these, the cause of death was directly attributed to systemic candidiasis.
With amphotericin B treatment, drug monitoring is not done as no therapeutic range has been recommended.[18]

Safety
Liposomal amphotericin B is less nephrotoxic and has fewer infusion related reactions than conventional amphotericin B (LOEI, GOR A).[15] However, the finding of reduced nephrotoxicity with liposomal amphotericin B needs to be interpreted with caution as significant heterogeneity was observed (I^2 = 59%).[11]
In a retrospective cohort study,[16] authors noted higher mortality in infants receiving amphotericin B lipid products as compared to conventional amphotericin B. The study, however, lacked clinical data regarding underlying illnesses though there were no significant differences in the mean gestation, birth-weight, age at onset of infection or serum creatinine. Authors discuss that they were unable to determine whether more critically ill infants with higher serum creatinine were selected for amphotericin B lipid products as only 17% of the infants had serum creatinine reported within 1 day of starting treatment. It is also interesting to note that in this study, while the overall mortality is higher for the group receiving amphotericin B lipid products, the 7-day, 14-day and 30-day mortality figures seem to be no different (mortality for conventional amphotericin B and amphotericin B lipid products respectively; 7-day: 7 and 6%, 14-day: 11 and 8%, 30-day: 14 and 13%).

Pharmacokinetics
Amphotericin B, in both its conventional and lipid formulation, has similar pharmacokinetics in neonates and children as in adults.[6] Wurthwein et al[8] conducted a pharmacokinetic study of amphotericin B **lipid complex** (ABLC) in 28 neonates (24–41 weeks gestation) with analysis of the drug concentration in blood, urine and CSF. The disposition of ABLC was similar to that observed in other age groups and weight was the only factor influencing clearance. No similar study on liposomal amphotericin B in the neonatal age group is available.
Although amphotericin B formulations are known to cause nephrotoxicity and may cause hepatotoxicity, reducing the dose in these disease states is not currently recommended.[19] If nephrotoxicity or hepatotoxicity is a significant concern, consider other antifungals.

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