Amphotericin B – Conventional

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). Amphotericin B – Conventional is also called Amphotericin B deoxycholate. The current TGA approved name is amphotericin B (amphotericin). Confusion among these products has led to fatal overdose as well as sub-therapeutic dosing.[1] Clinicians should liaise with local ID specialists when treating systemic fungal infections. Amphotericin B – Conventional is only available via Special Access Scheme (SAS) in Australia.
Indication	Treatment of invasive fungal infections by susceptible fungi including *Candida spp.*, *Aspergillus spp.* and *Cryptococcus* species.[2,17] *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.[3]
Drug Type	Polyene antifungal.
Trade Name	Fungizone.
Presentation	Vial contains 50 mg of amphotericin B.[4] It also contains sodium deoxycholate and sodium phosphate.
Dosage/Interval	0.5–1 mg/kg/dose **daily**.[5] 0.5–0.7 mg/kg/dose daily is recommended for *Candida* urinary tract infections including renal tract fungal balls.[5] 1 mg/kg/dose daily is recommended for *Aspergillus* systemic infection.[9] Liaise with ID specialists for further dose adjustments.
Route	Intravenous
Maximum Daily Dose	1 mg/kg/day.[5]
Preparation/Dilution	1. Reconstitute the 50 mg vial with 10 mL water for injection to make a concentration of 5 mg/mL. Shake the vial immediately until the solution is clear. Dilute 1 mL of the reconstituted solution with 49 mL of 5% glucose to make a concentration of 0.1 mg/mL.[4] 2. For fluid restricted patients: Reconstitute the 50 mg vial with 10 mL water for injection to make a concentration of 5 mg/mL. Shake the vial immediately until the solution is clear. Dilute 1 mL of the reconstituted solution with 11.5 mL of 5% glucose to make a concentration of 0.4 mg/mL.
Administration	IV infusion over 2–6 hours.[4] **IV line must be flushed with 5% glucose before and after the dose.** Do not infuse concentrations greater than 0.1 mg/mL through a peripheral line. Use a central venous catheter for 0.4 mg/mL concentration.[4]
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	Hypersensitivity to amphotericin B.
Precautions	Amphotericin B (conventional) has variable pharmacokinetics in neonates and this may lead to unexpected treatment failure or toxicity. Administer under close clinical supervision during the initial dosing. Anaphylaxis and respiratory distress have been reported in adults (though not in neonates). Renal impairment: Risk of nephrotoxicity. Concomitant use of corticosteroids and corticotropin (ACTH) should be avoided.[16]
Drug Interactions	Increased risk of nephrotoxicity if used concurrently with other nephrotoxic drugs e.g. aminoglycosides, vancomycin. Monitor renal function and relevant drug concentrations closely. Amphotericin B may enhance the toxicity of flucytosine by increasing its cellular uptake and impeding its renal excretion.[17] 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	Vial: Store at 2–8°C. Protect from light. Reconstituted solution: Stable for 24 hours below 25°C and for 1 week at 2–8°C. Do not use the reconstituted solution or infusion if cloudy or a precipitate is present. **Protect from light.** Diluted solution: Stable for 24 hours at 25°C. **Protect from light.** There is no need to protect from light during the infusion.
Storage	As above
Special Comments	The minimum infusion duration is 2 hours.[4] The osmolality of amphotericin B – conventional at a concentration of 0.1 mg/mL has been reported as 265–314.8 mOsm/kg.[18,19] If infusion-related, immediate reactions occur (e.g. fever, hypotension), duration of infusion may be increased to 6 hours. If total parenteral nutrition (TPN) or IV fluids are turned off during the infusion, consider monitoring of blood glucose. **If amphotericin B – conventional is used for *Candida* urinary tract infection including instances of renal tract fungal balls, a dose of 0.5–0.7 mg/kg/dose daily is suggested.[5] However, fluconazole may be a preferred agent in susceptible *Candida* urinary tract infections due to favourable pharmacokinetics and fewer side effects.[8]** Although amphotericin B formulations are known to cause nephrotoxicity and may cause hepatotoxicity, reducing the dose in these disease states is not currently recommended.[21] 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.[6,7] One small study (24 newborn infants) that compared conventional amphotericin B with fluconazole found fluconazole to have fewer side effects.[8] Australian 2014 consensus guidelines 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 susceptible to amphotericin B, whereas 5% of *C. albicans* and > 10% of *C. glabrata* are 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.[5] 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 – conventional: 0.5–1 mg/kg/dose daily for *Candida* systemic infection. They also recommend a dose of 0.5–0.7 mg/kg/dose daily for *Candida* urinary tract infections including renal tract fungal balls.[5] For *Aspergillus* systemic infection, a starting dose of 1 mg/kg/dose daily has been recommended.[9] Liposomal formulation is the preferred preparation for *Aspergillus* infections as higher doses can be administered. With amphotericin B treatment, drug monitoring is not done as no therapeutic range has been recommended.[20] **Safety** Amphotericin B – **c**onventional has increased risk of nephrotoxicity and infusion-related adverse reactions compared to liposomal amphotericin B (LOEI, GOR A).[10] In a study[11] performed in 56 neonates with *Candida* bloodstream infection (52 preterm, 36 extremely low birth-weight), 34 received **conventional** amphotericin B, 6 received **liposomal** amphotericin B and 16 received amphotericin B **colloidal dispersion**. No significant differences in mortality, resolution of fungaemia and adverse effects were seen. In a retrospective cohort study[12] 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 (conventional) has variable pharmacokinetics in neonates and this may lead to unexpected treatment failure or toxicity.[13] A pharmacokinetic study in 10 children (including 5 premature infants) suggested a smaller volume of distribution and higher elimination clearance as compared to adults.[14] This may explain the fact that amphotericin B is better tolerated in neonates as compared to adults. Interpatient variability was, however, marked. Another pharmacokinetic study[15] also noted extreme inter-individual variability for the half-life, volume of distribution and clearance. Cerebrospinal fluid (CSF) concentrations were 40% to 90% of serum values (in contrast to adults where CSF penetration of amphotericin B is poor).[15] Although amphotericin B formulations are known to cause nephrotoxicity and may cause hepatotoxicity, reducing the dose in these disease states is not currently recommended.[21] If nephrotoxicity or hepatotoxicity is a significant concern, consider other antifungals.

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