Alert
The Antimicrobial Stewardship Team has listed this drug as: Restricted.

Amphotericin B is available in 4 forms: Amphotericin B-conventional, Amphotericin B-liposomal, Amphotericin B [phospholipid] 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). Amphotericin B-conventional is only available via Special Access Scheme (SAS) in Australia.

Confusion among these products has led to fatal overdose as well as sub-therapeutic dosing. Clinicians should liaise with local ID specialists when treating systemic fungal infections. Refer to Amphotericin B-liposomal formulary if using amphotericin – B liposomal.

### Indication
Treatment of invasive fungal infections by susceptible fungi including *Candida spp.*, *Aspergillus spp.* and *Cryptococcus* species. *Candida lusitaniae* and *A. terreus* are resistant.

### Action
Fungicidal agent that binds with a cytoplasmic membrane ergosterol on the organism’s surface, causing cell death by increasing cell membrane permeability.

### Drug type
Polyene antifungal.

### Trade name
Fungizone.

### Presentation
50 mg of amphotericin B vial.

### Dose
0.5–1 mg/kg/dose daily.

0.5–0.7 mg/kg/dose daily is recommended for *Candida* urinary tract infections including renal tract fungal balls.

1 mg/kg/dose daily is recommended for *Aspergillus* systemic infection. Liaise with ID specialists for further dose adjustments.

### Dose adjustment
Maximum dose 1 mg/kg/day.

Total cumulative dose

### Route
IV

### Preparation
Add 10 mL water for injection to 50 mg vial to make a 5 mg/mL solution. Shake the vial immediately until the solution is clear.

**FURTHER DILUTE**

Draw up 1 mL (5 mg of Amphotericin B – Conventional) of the above solution and add 49 mL of 5% glucose to make final volume of 50 mL with a final concentration of 0.1 mg/mL. 

**For fluid restricted patients with central IV access**

Add 10 mL water for injection to 50 mg vial to make a 5 mg/mL solution. Shake the vial immediately until the solution is clear.

**FURTHER DILUTE**

Draw up 1 mL (5 mg of Amphotericin B – Conventional) of the above solution and add 11.5 mL of 5% glucose to make final volume of 12.5 mL with a final concentration of 0.4 mg/mL.

### Administration
IV infusion over 2–6 hours. IV line must be flushed with 5% glucose before and after the dose. Peripheral IV access for 0.1 mg/mL concentration. Central IV access for > 0.1 mg/mL concentration.

### 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).

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).
| 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. Corticosteroids and diuretics: May enhance the hypokalaemic effect of amphotericin B. |
| 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. |
| Excipients | Sodium deoxycholate and sodium phosphate |
| Special comments | The minimum infusion duration is 2 hours. The osmolality of amphotericin B – conventional at a concentration of 0.1 mg/mL has been reported as 265–314.8 mOsm/kg. 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. However, fluconazole may be a preferred agent in susceptible Candida urinary tract infections due to favourable pharmacokinetics and fewer side effects. Although amphotericin B formulations are known to cause nephrotoxicity and may cause hepatotoxicity, reducing the dose in these disease states is not currently recommended. If nephrotoxicity or hepatotoxicity is a significant concern, consider other antifungals. |
| Evidence | Efficacy | There are no adequately powered, comparative trials of different antifungal therapies for invasive fungal infection in the neonatal setting. One small study (24 newborn infants) that compared conventional amphotericin B with fluconazole found fluconazole to have fewer side effects. 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. 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 (LOIII, 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 – conventional has increased risk of nephrotoxicity and infusion-related adverse reactions compared to liposomal amphotericin B (LOEI, GOR A).10

In a study11 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 study12 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 study15 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.

Practice points

References

VERSION/NUMBER DATE
Original 1.0 17/07/2017
Current 2.0 5/01/2021
REVIEW (5 years) 5/01/2026

Authors Contribution

Original author/s Rajesh Maheshwari, Srinivas Bolisetty
Evidence Review David Osborn
Expert review Brendan McMullan, Tony Lai
Nursing Review Eszter Jozsa, Kirsty Minter
Pharmacy Review Jing Xiao, Ushma Trivedi, Carmen Burman
ANMF Group contributors Ansar Kunjunju, Michael Hewson, Rahul Udaya Prasad, Nilkant Phad, Bhavesh Mehta, John Sinn, Michelle Jenkins, Thao Tran, Wendy Huynh, Helen Huynh
Final editing and review of the original Ian Whyte
Electronic version Cindy Chen, Ian Callander
Facilitator Srinivas Bolisetty