UWHC Guidelines For the Use Of Lipid-Based Amphotericin B Products In Adults and Children

Guidelines developed by UWHC Center for Drug Policy (CDP)
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A. Background
The newer lipid-based formulations of amphotericin B are less likely to cause elevations in serum creatinine than conventional amphotericin B deoxycholate (AmB). Available studies indicate comparable efficacy. The lipid-based formulations are usually used as second-line agents because they are much more expensive than the conventional formulation. Currently at UWHC, daily drug costs for a 70-kg patient are $13.54 for amphotericin B and $423.15 for liposomal amphotericin B (AmBisome®). Our current lipid-based formulary choice is AmBisome®. Criteria for switching patients to AmBisome® include conventional amphotericin B-induced renal toxicity, risks for or signs of renal toxicity, intolerance to AmB, and progression of the infection despite adequate doses of the conventional formulation.

B. Appropriate Indications for Use of AmBisome®.
Conventional amphotericin B deoxycholate (AmB) is the first-line amphotericin product at the UWHC. Several new antifungal agents, including voriconazole and echinocandins may have a role in the primary management of invasive filamentous fungal infections. Liposomal amphotericin (AmBisome®) should be reserved for use as a second-line agent in the treatment of documented serious, deep fungal infections caused by organisms such as Candida, Cryptococcus, and Aspergillus. Criteria for using AmBisome® instead of AmB include one or more of the following circumstances:

1.0 Baseline renal impairment, as defined below.
   1.1 Adults:
      1.1.1 Baseline creatinine clearance less than 30 mL/min or less than 50 mL/min in patients concurrently taking other nephrotoxic drugs like cyclosporine, tacrolimus, aminoglycosides, foscarnet; or past or current use of cisplatin.
      1.1.2 Baseline creatinine greater than 2.5 mg/dL or 2.0 m/dL in patients concurrently taking other nephrotoxic drugs.
      1.1.3 Anticipated extended course of therapy where renal toxicity would be highly anticipated.

1.2 Children:
   1.2.1 Baseline creatinine clearance less than 30 mL/min or less than 50 mL/min in patients concurrently taking other nephrotoxic drugs like cyclosporine, tacrolimus, aminoglycosides, foscarnet; or past or current use of cisplatin or baseline serum creatinine as outlined in Table 1.

Table 1. Baseline Serum Creatinine For AmBisome® Use In Children

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Normal SCr</th>
<th>Baseline SCr For Initiation Of AmBisome®</th>
</tr>
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<tbody>
<tr>
<td>≤ 2</td>
<td>~ 0.2 mg/dL</td>
<td>0.4 mg/dL</td>
</tr>
<tr>
<td>3</td>
<td>~ 0.3 mg/dL</td>
<td>0.6 mg/dL</td>
</tr>
<tr>
<td>4</td>
<td>~ 0.4 mg/dL</td>
<td>0.8 mg/dL</td>
</tr>
<tr>
<td>5</td>
<td>~ 0.5 mg/dL</td>
<td>1 mg/dL</td>
</tr>
<tr>
<td>6</td>
<td>~ 0.6 mg/dL</td>
<td>1.2 mg/dL</td>
</tr>
<tr>
<td>7</td>
<td>~ 0.7 mg/dL</td>
<td>1.4 mg/dL</td>
</tr>
<tr>
<td>&gt; 8</td>
<td>~ 0.8 mg/dL</td>
<td>1.5 mg/dL</td>
</tr>
</tbody>
</table>
1.3 The attending physician will evaluate transplant patients on a case-by-case basis.

2.0 Development of renal toxicity during AmB treatment

2.1 Adults:
   2.1.1 Decrease in creatinine clearance to less than 30 mL/min or less than 50% of the baseline value.
   2.1.2 An increase in serum creatinine to 2.5 mg/dL or a doubling of the baseline value.

2.2 Children:
   2.2.1 Decrease in creatinine clearance to less than 30 mL/min or less than 50% of the baseline value or a sustained increase in serum creatinine as described in Table 2.

Table 2. Change In Serum Creatinine Indicating a Need To Switch To AmBisome®

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Increase in SCr from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>0.2 mg/dL maintained for 2 days</td>
</tr>
<tr>
<td>4 to 12</td>
<td>0.3 mg/dL maintained for 2 days</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>0.5 mg/dL maintained for 2 days</td>
</tr>
</tbody>
</table>

2.3 Note: If serum creatinine begins to rise, check the following points before switching products:
   2.3.1 Up to 500 mL of IV saline should be given 1-2 hours prior to each AmB infusion (10 mL/kg up to 500 mL for children).
   2.3.2 Nephrotoxicity can sometimes be decreased or delayed by every-other-day administration.
   2.3.3 If appropriate, a dose reduction may be considered.

3.0 Severe, systemic intolerance to amphotericin B infusions despite adequate premedication and hydration.

3.1 For the first few infusions, pre-medication, including acetaminophen, diphenhydramine and hydrocortisone, may be administered to prevent severe chills, fever, dyspnea and other infusion-related events; tolerance to these effects often develops.

3.2 Patients should be adequately hydrated for each infusion, with 250 - 1000 mL 0.9% saline IV given prior to and following each infusion. Apparent intolerance may be decreased by every-other-day administration, or if clinically feasible, a decrease in dose.

3.3 Meperidine 25 mg IV (for adults) every 15 minutes as needed x4 doses may be administered to treat rigors.

3.4 In rare instances, severe reactions can persist in spite of pre-medication, and switching to a different formulation may be reasonable. Note that documented cases of intolerance to two different lipid formulations have been resolved by use of the conventional formulation.

4.0 Failure of conventional amphotericin B

4.1 Lack of clinical improvement, persistent positive cultures, progression or dissemination of disease after 500 mg in adults or 7 mg/kg in children of conventional amphotericin B has been given.

C. Inappropriate Uses

1.0 Use in patients with a documented fungal infection amenable to treatment with an alternate antifungal agent, other than AmBisome®.

2.0 Patients on dialysis. These patients should be treated with conventional amphotericin B.

D. Use of Liposomal Amphotericin B (AmBisome®)
1.0 Consideration should be given to alternate antifungals including voriconazole (Vfend®), http://www.hosp.wisc.edu/CRIT/guides/formulary/voriconazole.htm or micafungin (Mycamine®) http://www.hosp.wisc.edu/CRIT/guides/formulary/caspofungin.htm before prescribing liposomal amphotericin B.

2.0 Use of liposomal amphotericin B requires approval by Infectious Diseases.

2.1 The physician wishing to prescribe AmBisome® for an adult patient will contact pager #3333 between the hours of 0700 and 2200 to reach the ID fellow or attending ID physician on call. If ID approval is given, the ordering physician will then inform the unit pharmacist that approval has been given. A formal consult is not required, but the pharmacist or PHA should document the name of the authorizing Infectious Diseases physician in the instructions field when entering the order into HealthLink.

2.2 The physician wishing to prescribe AmBisome® for a pediatric patient will contact the pediatric Infectious Diseases physician on call between the hours of 0700 and 2300 for approval of the order for AmBisome®. If ID approval is given, the ordering physician will then inform the unit pharmacist that approval has been given. A formal consult is not required, but the pharmacist or PHA should document the name of the authorizing Infectious Diseases physician in the instructions field when entering the order into HealthLink.

2.3 In the event of an emergency or if there is an expected delay in the approval process, such as an order written between 2200 and 0700, a single dose of the drug may be dispensed by the Pharmacy without ID approval. Subsequent doses will not be dispensed until ID approval has been obtained.

3.0 Patients may be potential candidates for liposomal amphotericin B under the following circumstances:

3.1 Liposomal amphotericin B is the amphotericin product of choice to treat Histoplasma or Cryptococcus infections in AIDS patients, and to treat rhinocerebral mucormycosis or visceral leishmaniasis.

3.2 The dose for treatment of systemic fungal infections is 3-5 mg/kg/day IV. The dose for treatment of cryptococcal meningitis is 6 mg/kg/day IV. The dose for treatment of visceral leishmaniasis is 3 mg/kg/day IV on days 1-5, 14 and 21 in immunocompetent patients, and 4 mg/kg/day IV on days 1-5, 10, 17, 24, 31 and 38 in immunocompromised patients. Higher doses of AmBisome® have not been shown to be more effective than the doses noted above.(reference 5 vs 10 mg/kg).

References:


UWHC Guidelines for Use of Antifungal Therapy


IDSA Guidelines for the treatment of Candidiasis: http://www.journals.uchicago.edu/doi/pdf/10.1086/596757