Appendix E: UWHC Guidelines for the Appropriate Use of Antifungal Drugs

Guidelines developed by UWHC Antimicrobial Use Subcommittee and the Drug Policy Program (DPP)
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Approved By P&T Committee: September 2003
Last Reviewed: February 2007
Next Scheduled Review Date: June 2011

A. Management of Patients with Documented or Probable Invasive Fungal Infections

1.0 Candida Infections

1.1 There are no data to indicate that lipid-associated IV amphotericin B is superior therapeutically to conventional amphotericin B in adequate doses (0.3-0.6 mg/kg/day).

1.2 For Candida bloodstream infections, echinocandins may be marginally superior to conventional IV amphotericin B.\(^1^,^2^,^3\) Three to ten days of echinocandin therapy with stepdown to oral fluconazole may be considered as one standard of care.

1.3 For C. albicans infections, IV fluconazole (400 – 800 mg/day) generally gives results therapeutically comparable to conventional IV amphotericin B (and presumably echinocandin).\(^4^,^5\)

1.4 For non-albicans Candida infections, fluconazole may fail because of reduced susceptibility.\(^6\) Susceptibility testing for Candida glabrata isolated from sterile body sites is automatically sent for susceptibility testing. Other testing is available upon request. An echinocandin or IV amphotericin B may be preferred.\(^7^,^8\)

1.5 Voriconazole has recently been approved for the treatment of candidemia, but clinical experience is limited; published data available at the time of approval of this document are limited to salvage therapy.\(^9\)

2.0 Deep Aspergillus Infections

2.1 There are no data that conclusively show the lipid-associated amphotericin preparations are therapeutically superior to conventional IV amphotericin B in full doses (≥ 1 mg/kg/day).\(^10\) However, since it is essential to use full dose IV amphotericin B for filamentous fungal infections (≥1 mg/kg/d), a dosage which produces substantial nephrotoxicity, in general, lipid-associated preparations of amphotericin B (5 mg/kg/day) are preferable for documented filamentous fungal infection, especially deep Aspergillus or Zygomycetes infections.

2.2 Voriconazole appears to be superior to all IV amphotericin B products for invasive Aspergillus infections and is recommended for initial therapy of probable or documented invasive Aspergillus infections.\(^11\) Echinocandins have also been shown to be effective for invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy.\(^12\)
2.3 Recent animal data and some recent clinical data suggest that for documented or highly suggestive invasive *Aspergillus* infections, the *combination* of voriconazole with an echinocandin may be therapeutically superior to the use of either drug alone.\(^{13-17}\) However, a randomized trial by the national mycoses study group is in progress and results should be available shortly in 2010. This trial limits combination therapy to 14 days, and not indefinitely.

2.4 General comments regarding Lipid-based Amphotericin products: There are no data to suggest that liposomal amphotericin B (AmBisome\(^{8}\)) is superior to amphotericin B lipid complex (Abelcet\(^{6}\), ABLC),\(^{18}\) except for intracranial fungal infections or histoplasmosis,\(^{24}\) where AmBisome\(^{8}\) may be more effective.\(^{19}\) There are limited data that indicate that AmBisome\(^{8}\) is slightly less nephrotoxic than amphotericin B lipid complex. AmBisome\(^{8}\) is the current UWHC formulary lipid-associated amphotericin product at this time.

3.0 CNS Cryptococcal Infections

3.1 In general, an amphotericin product plus flucytosine remains the regimen of first choice.\(^{20,21}\)

3.2 For patients unable to tolerate this regimen (e.g., patients with advanced AIDS), fluconazole 400-800 mg/day is recommended.\(^{22}\)

3.3 Echinocandins are *not* effective for treatment of cryptococcal infection.

3.4 Data suggest voriconazole or posaconazole may be useful for fluconazole failures but it should not be used as primary therapy.\(^{23}\)

3.5 For indefinite suppressive therapy (e.g., in advanced AIDS), fluconazole is recommended.\(^{24}\)

4.0 Other filamentous fungal infections/endemic mycoses

4.1 Some fungal species, such as *Zygomycetes, Fusarium* or *Scedosporium*, are resistant to amphotericin B or voriconazole.\(^{25}\) In general, with infections caused by these organisms, *in vitro* susceptibility testing is strongly recommended and ID consultation should be sought.

4.2 For treatment of histoplasmosis, blastomycosis and coccidiomycosis, the treatment of choice for life-threatening infections remains an amphotericin-based product, and AmBisome\(^{8}\) is preferred at this time for histoplasmosis.\(^{26}\) For less severe infections or for step-down therapy, use of itraconazole for histoplasmosis and blastomycosis is acceptable. For coccidiomycosis, fluconazole should be utilized.\(^{21}\)

4.3 Data supporting the use of voriconazole or posaconazole for the treatment of endemic mycosis are lacking, but there is some accumulating evidence that voriconazole may be effective.

4.4 Posaconazole has been approved for prophylaxis of invasive fungal infections in patients with hematologic malignancies. It has *in vitro* activity against *Zygomycetes*, and may be considered for adjunctive therapy with amphotericin for such infections under the guidance of an infectious disease specialist.\(^{27,28}\)
B. Antifungal Prophylaxis for BMT and Hematologic Malignancies

1.0 For allogenic BMT patients, fluconazole prophylaxis has been shown to reduce the incidence of deep Candida infections.40-42

2.0 Itraconazole may be more effective than fluconazole for prevention of invasive fungal infections but is associated with more frequent GI side effects.43

3.0 For patients with hematologic malignancies or solid tumors, no study has shown a clear benefit of antifungal prophylaxis. High-risk patients with prolonged neutropenia, however, can be individually considered for this strategy.44

4.0 Micafungin has been approved for prophylaxis for stem cell transplant recipients, but the benefit of prophylaxis with this or other echinocandin must be weighed against the potential loss of this class of drug for therapeutic purposes.45

5.0 Posaconazole has been approved for prophylaxis for patients with hematologic malignancies. While preliminary data is encouraging, difficulties with drug absorption and drug interactions may not make this a suitable prophylaxis alternative for all patients. Voriconazole should not be automatically substituted for patients having difficulty with posaconazole.46,47

6.0 Patients with hematologic malignancies with significant GVHD >Grade 3 may be considered candidates for prophylaxis with posaconazole, or occasionally voriconazole, although evidence based medicine for the later is lacking.48,49

C. Empiric Antifungal Therapy for the Management of Patients with Febrile Neutropenia

1.0 In patients with granulocytopenia (<500/mcL) who have had persistent fever for more than 3-5 days despite empiric antibiotic therapy (cefepime or piperacillin/tazobactam, with or without tobramycin or ciprofloxacin), the addition of an antifungal drug to the empiric regimen is desirable and can reduce mortality from occult deep fungal infection.29 These patients should ideally be screened for invasive fungal infections through serological and radiographic means.49

Patients may be stratified by their risk of invasive fungal infections as noted below.

Low risk = not high risk

High risk = febrile patient with one or more of the following:
- Any patient with greater than 21 days of persistent neutropenia after cytotoxic chemotherapy
- Stem cell transplantation with neutropenia of greater than 5 days
- Patients with relapsed leukemia undergoing reinduction therapy with neutropenia/fever greater than 5 days
- Stem cell transplant with GVHD >Grade 3 with or without neutropenia/fever
- Any patient with greater than 7 days of neutropenia, unresponsive to 7 days of azole empiric therapy, with high suspicion of filamentous fungal infection

2.0 Conventional IV amphotericin B (at a dose of 0.5 mg/kg) and lipid-based amphotericin products (at a dose of 3-5 mg/kg) are both effective.30,31 However, in patients who have not been receiving fluconazole prophylactically, fluconazole or itraconazole appear to give comparable results32,33 and voriconazole may be considered for high-risk patients.
3.0 There is no proven role for the use of voriconazole for routine empiric therapy of neutropenic fever. In a recent multi-center randomized trial, voriconazole was marginally more effective than amphotericin B in high risk patient subgroups only and statistically inferior in other subgroups.34-36

4.0 Other studies have shown that an echinocandin may be an effective alternative to lipid-based amphotericin products.37,38 Echinocandins may be considered for use at UWHC for certain high risk patients with extensive azole experience as outlined below. Use of echinocandins must be weighed against the future risk of drug resistance.39

In trying to decide on the optimal antifungal regimen, also assess whether patients have had prior azole antifungal therapy or prophylaxis (defined as greater than 14 days of the equivalent of 200 mg of fluconazole or itraconazole, 400 mg of voriconazole or 600mg of posaconazole in the past 3 months). Prophylaxis with voriconazole or posaconazole makes the development of invasive fungal infection much less likely.50 Specifically also assess whether patients have been receiving posaconazole prophylaxis in a reliable fashion, including assessment of drug levels. Prophylaxis regimens should be discontinued if therapeutic choices are chosen. The suggested regimens are:

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prior azole therapy:</strong></td>
<td>echinocandin, voriconazole</td>
</tr>
<tr>
<td>fluconazole, itraconazole</td>
<td>AmBisome®</td>
</tr>
<tr>
<td><strong>Prior fluconazole, itraconazole</strong></td>
<td>echinocandin or AmBisome®</td>
</tr>
<tr>
<td>echinocandin or AmBisome®</td>
<td>echinocandin or AmBisome®</td>
</tr>
<tr>
<td><strong>Prior posaconazole</strong></td>
<td>no change</td>
</tr>
<tr>
<td>no change</td>
<td>no change or AmBisome®</td>
</tr>
<tr>
<td><strong>Prior voriconazole</strong></td>
<td>posaconazole or AmBisome®</td>
</tr>
<tr>
<td>posaconazole or AmBisome®</td>
<td>AmBisome®</td>
</tr>
</tbody>
</table>
## D. Cost Comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (70 kg patient)</th>
<th>Cost per day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>1 mg/kg/day IV daily</td>
<td>$13.54</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B Liposomal</td>
<td>5 mg/kg/day IV daily</td>
<td>$423.15</td>
<td>Requires ID Section approval</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>5 mg/kg/day IV daily</td>
<td>$253.65</td>
<td>Nonformulary; requires ID approval</td>
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<tr>
<td>Anidulafungin</td>
<td>Load – 200 mg IV</td>
<td>$347.86</td>
<td>Nonformulary; requires ID Section approval</td>
</tr>
<tr>
<td></td>
<td>Maintenance – 100 mg IV</td>
<td>173.93</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Load – 70 mg IV</td>
<td>$338.72</td>
<td>Nonformulary; requires ID Section approval</td>
</tr>
<tr>
<td></td>
<td>Maintenance – 50 mg IV</td>
<td>326.00</td>
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</tr>
<tr>
<td>Micafungin</td>
<td>100 mg IV daily</td>
<td>$86.74</td>
<td>Requires ID Section approval</td>
</tr>
<tr>
<td></td>
<td>150 mg IV daily</td>
<td>130.11</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Load – 400 mg IV</td>
<td>$5.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance – 200 mg IV</td>
<td>2.68</td>
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<tr>
<td>Fluconazole</td>
<td>200 mg PO daily</td>
<td>$0.14</td>
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<tr>
<td>Itraconazole</td>
<td>Load – 200 mg PO TID</td>
<td>$33.24</td>
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<tr>
<td></td>
<td>Maintenance – 200 mg PO BID</td>
<td>22.16</td>
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<tr>
<td>Posaconazole</td>
<td>200 mg PO Q8h</td>
<td>$82.28</td>
<td>Requires ID Section approval except for use according to the standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>operating procedures of the Hematology Section</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Load – 6 mg/kg IV Q12h x 2</td>
<td>$485.31</td>
<td>Requires ID Section approval</td>
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<tr>
<td></td>
<td>doses</td>
<td>$323.54</td>
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<tr>
<td></td>
<td>Maintenance – 4 mg/kg IV Q12h</td>
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</tr>
<tr>
<td>Voriconazole</td>
<td>200 mg PO BID</td>
<td>$82.74</td>
<td>Requires ID Section approval</td>
</tr>
</tbody>
</table>
References:


